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The BULLETIN of the ASSOCIATION for the STUDY of INTERNAL SECRETIONS

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CONTENTS

ADRENALIN VASODILATOR MECHANISMS. By Frank A. Hartman, Toronto. 1

A NOTE ON THE USE OF CORPUS LUTEUM TO PREVENT THE PAINFUL BREASTS OF MENSTRUATION. By H. Lisser, San Francisco. . . 12

A STUDY OF THE SYMPTOMS OF EXOPHTHALMIC GOITRE. By F. M. Pottenger, Monrovia, Cal. 16

AN ENDOCRINE PROBLEM 40

ENDOCRINOLOGIA, PATOLOGIA E CLINICIA——A CRITIQUE (Book Review) By G. Vercellini, St. Paul 42

THE LITERATURE ON THE INTERNAL SECRETIONS. Containing 79 Titles and Articles Reviewed

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"In this last class, dysmenorrhea should be especially included. In my own practice I have observed, in a truly extraordinary manner, the cure or relief of many such cases through the medium of this type of organotherapy. My best results, however, have been gained in the administration of corpus luteum for the relief of the severe nervous symptoms attendant upon the menopause of both the physiological and artificial varieties and the functional amenorrhea of young women."—Dr. Adam P. Leighton, Jr., The American Journal of Obstetrics and Diseases of Women and Children, November, 1915, page 878.

"Mrs. P. D., aged 35, married twelve years, was the mother of six children. Menstruation was regular. She complained of nervousness, irritability, inability to carry on the household duties, and depression. All symptoms were worse at the menstrual period. This patient was first seen in October, 1911. To nine-tablet doses per diem she responded at once; reported that she had not felt so well in years. After one month of this treatment, the dosage was reduced to three tablets a day and continued another month. She then gave it up altogether, and is still feeling perfectly well."—Dr. Curtis F. Burnam, The Journal A. M. A., August 31, 1912; page 698.

(Complete and additional reports upon request)

Lutein Tablets

(Corpus Luteum)

5 grain, 50 in a tube
2 grain, 100 in a tube

TABLE OF CONTENTS

ADRENALIN VASODILATOR MECHANISMS. By Frank A. Hartman, Toronto 1

A NOTE ON THE USE OF CORPUS LUTEUM TO PREVENT THE PAINFUL BREASTS OF MENSTRUATION. By H. Lisser, San Francisco.... 12

A STUDY OF THE SYMPTOMS OF EXOPHTHALMIC GOITRE. By F. M. Pottenger, Monrovia, Cal..... 16

AN ENDOCRINE PROBLEM..... 40

ENDOCRINOLOGIA, PATOLOGIA E CLINICIA. (Book Review.) By G. Vercellini, St. Paul..... 42

THE LITERATURE ON THE INTERNAL SECRETIONS..... 51

THE THYROID HORMONE AND ITS RELATION TO THE OTHER DUCTLESS GLANDS. By E. C. Kendall, Rochester, Minn..... 81

THE PITUITARY BODY AND POLYURIA. By B. A. Houssay, Buenos Aires 94

ON THE SEASONAL VARIATION IN THE IODINE CONTENT OF THE THYROID GLAND. By Frederic Fenger, Chicago..... 98

CONFUSIONAL INSANITY AND THE OVARIES: A CASE HISTORY. By George H. Hoxie, Kansas City..... 101

DIABETES INSIPIDUS. By Ketil Motzfeldt, Christiania..... 112

VASCULAR CHANGES PRODUCED BY ADRENALIN IN VERTEBRATES. By Frank A. Hartman, Leslie G. Kilborn and Ross S. Lang, Toronto 122

SUPPURATION OF GOITROUS THYROID FOLLOWING ADMINISTRATION OF THYROID EXTRACT: A CASE REPORT. By Edward A. Tracy, Boston 143

A CASE OF PARATHYROID INSUFFICIENCY. By Arthur L. Hertz, London 145

THE RELATION OF THE ADRENAL GLANDS TO SUGAR METABOLISM.. 149

THYROID AND THYMUS. (Book Review)..... 153

THE LITERATURE ON THE INTERNAL SECRETIONS..... 157

A NEW PLURIGLANDULAR COMPENSATORY SYNDROME. By Walter Timme, New York..... 209

IS THERE A THYMIC HORMONE? By E. R. Hoskins, New York.. 241

ACTIVE COOPERATION BETWEEN THE PHYSIOLOGIST AND THE CLINICIAN AND COMPARATIVE ANALYSIS OF CO-ORDINATED DATA IN THE STUDY OF THE INTERNAL SECRETIONS. By C. E. de M. Sajous, Philadelphia 258

IODIN AS THE ACTIVE PRINCIPLE OF THE THYROID GLAND. By W. W. Swingle, Princeton, N. J..... 283

THE EFFECT OF THE X-RAY UPON THE RESPONSE OF TADPOLES TO THYROID STIMULATION. By Carey P. McCord and Carlton J. Marinus, Detroit 289

THE USE OF ADRENAL PRODUCTS IN ADDISON'S DISEASE. By Judson Daland, Philadelphia 301

THE LITERATURE ON THE INTERNAL SECRETIONS..... 309

370871

Cyclic Changes in the Interstitial Cells of the Ovary and Testis in the Woodchuck (Marmota Monax). By A. T. Rasmussen, Minneapolis 352

The Role of the Thymus in Pediatrics. By Murray B. Gordon, Brooklyn 405

The Newest "Hormone." By Swale Vincent, Winnipeg..... 421

A Case of Myxedema With Tumor of Pituitary Body and Lesions of Other Endocrine Organs. By W. H. Good and A. G. Ellis, Philadelphia..... 431

Some Points of Contact Between Endocrinology and Gynecology. By Emil Novak, Baltimore..... 438

Hormone Control of Renal Function..... 447

The Endocrine Glands in the Insane..... 452

Etiology of Graves' Disease..... 456

The Adrenin Test for Thyroid Disorders..... 460

Adrenin and Arsphenamine..... 467

The Literature on the Internal Secretions..... 469

ENDOCRINOLOGY:

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JANUARY—MARCH, 1918

ADRENALIN VASODILATOR MECHANISMS

By Frank A. Hartman

(From the Laboratory of Physiology, University of Toronto.)

It is well known that adrenalin causes constriction of arteries and that it does so by stimulation of myoneural junctional tissue. Moreover as a result of this constriction large doses of adrenalin produce a marked rise in blood pressure. Due to these facts the idea has prevailed that adrenalin vasomotor effects are essentially constrictor. Until lately we have been led to believe that adrenalin acts thus on all of the vessels except those without constrictor innervation. Even though it has been shown by a number of investigators recently that adrenalin causes active vasodilatation in the blood vessels of certain areas, the opinion is still held in many quarters that this reaction is exceptional. We will attempt to show that vasodilatation is the usual response in certain areas of the body when moderate doses of adrenalin are administered, and that this may be due to stimulation of certain structures located neither in the central nervous system nor at the extreme periphery.

E.H.

Cannon and Lyman (1) demonstrated that cats respond to small doses of adrenalin (intravenous) by a fall in blood pressure in a majority of cases. To be sure other more or less isolated observations of this sort had been made previously, but the credit belongs to them for establishing the fact. Because this was opposed to the generally accepted idea of adrenalin action it appeared attractive for further research. An attempt was made by me to account for the fall in blood pressure. By tying off the arteries of the splanchnic area or of the head and limb area and then determining the blood pressure response to adrenalin, I was led to the discovery that there was a shifting of the blood from the splanchnic area to the outlying skeletal muscles (2). This was accomplished by active dilatation of skeletal muscle areas attended simultaneously by active constriction of the splanchnic area. At the same time it was observed by use of the nasal plethysmograph that the nasal mucosa constricted.

Later, Hoskins, Gunning and Berry (3) using the plethysmographic method, confirmed my observation that there was active dilatation in the "peripheral" regions, but they went further and demonstrated that the skin constricts while the muscle dilates. Hoskins and Gunning (4) and ourselves (5) working independently made a study of the spleen, kidney and intestine by the use of oncometers. On the whole the observations of both of us agreed with the first observations on the differential action of adrenalin (2) i.e. depressor doses of adrenalin cause constriction of the splanchnic area. However we did differ from each other to a certain extent in our findings on the intestine. While Hoskins and Gunning

frequently obtained dilatation of the intestine with small doses we found constriction to be the more common and that dilatation usually resulted from larger doses and was preceded by constriction.

It is now well established that the blood vessels of certain areas of the body do actively dilate with the intravenous injection of moderate doses of adrenalin. The question next arose as to the place of action of the adrenalin in causing this dilatation. Was it due to stimulation of possible sympathetic vasodilator endings? Our first evidence opposed to this view was obtained in the study of vasodilatation in the intestine. Destruction of the semilunar and superior mesenteric ganglia usually prevented the dilatation (5). This indicated that the seat of stimulation must be either in these ganglia or else at some place in the central nervous system. We next studied the effect on the adrenalin response of cutting the nerves to a limb. Gruber (6) has shown that dilatation does not occur in a limb freshly cut off from the central nervous system. We found that this prevented active dilatation from adrenalin. This evidence appeared to indicate some central nervous effect or at least that the mechanism for adrenalin dilatation was not located in the nerve endings.

We proved in another way that the dilatation was not the result of stimulating "sympathetic vasodilator nerve endings" (7). In the case of the intestine, a short loop in a large dog was prepared for the oncometer and then carefully dissecting out the vein and artery supplying this loop so as to avoid injury to the nerves, these were tied off and cannulae inserted for perfusion. This loop was now kept alive by perfusion with oxygenated Ringer's solution at a

temperature of 37° to 38° C. Its only functional connection with the rest of the animal was by the nerves. Placed in an oncometer any changes in volume could be observed and recorded by means of a Brodie's bellows. We found that suitable doses of adrenalin injected into the jugular vein caused dilatation in the perfused loop. These doses were often large enough to cause a rise in blood pressure.

In a similar manner the active adrenalin vasodilatation of the limb was proved to be due to some mechanism far removed from the vessels affected. A hind limb placed in a plethysmograph had its circulation cut off by clamping the abdominal aorta well above the bifurcation. The part was immediately perfused with warm oxygenated Ringer's solution through a cannula inserted into the common iliac artery, the outlet being the corresponding vein. Small doses of adrenalin injected into the jugular vein were able to cause dilatation of the perfused limb. It seemed from these experiments that some central nervous mechanism must be involved in the vasodilatation from adrenalin.

Absence of the Mechanisms in the Central Nervous System

We attempted to locate these mechanisms in the central nervous system by destroying various portions, testing for the presence of the mechanism in each case by the plethysmographic method.

Decerebration did not interfere with either the intestinal or limb mechanism, nor did it prevent the fall in blood pressure from adrenalin. However, just as soon as the medulla was injured or destroyed there was a reversal in the blood pressure response. In spite of this both the hind limb mechanism and

the intestinal mechanism were active. Where there was any doubt as to this, the limb and intestine were tested by the perfusion method.

We destroyed more and more of the spinal cord and still obtained action from the mechanisms. If the intestinal mechanism were located in the central nervous system, it would have to be in the region where the splanchnic nerves left the spinal cord, as destruction of the brain and cord above did not prevent action. However complete destruction of the brain and spinal cord did not prevent intestinal vasodilatation from adrenalin as determined by the perfusion method. Therefore we were mistaken in presuming the location of the intestinal mechanism to be in the central nervous system.

Investigating in a similar manner we found that the adrenalin vasodilator mechanism for the hind limb is not located in the central nervous system. Active dilatation of a perfused hind limb with intact nervous connection could be obtained when adrenalin was injected into the jugular vein even after complete destruction of the sacral, lumbar and lower half of the thoracic cord.

Location of the Intestinal Mechanism*

If the intestinal mechanism is not located in the central nervous system it might be in the sympathetic ganglia, for it was by destruction of these that intestinal vasodilator effects were either prevented or considerably reduced. We were able to demonstrate after the following manner that this is one location of the mechanism for the intestine. To eliminate peripheral effects, perfused loops of intestine

*The original work included in this and the following section was done in collaboration with L. G. Kilborn and L. McP. Fraser.

were used as already described. All splanchnic nerve fibres were cut and in some cases the vagi. Six dogs were studied by this method. In every animal adrenalin injected into the jugular vein caused dilatation of the perfused loop of intestine. Cutting the nerves between the ganglia and the loop prevented these effects.

Nicotine should reduce the adrenalin vasodilatation in the intestine, if the sympathetic ganglia control such action. Nicotine was used for this purpose in four cats. In three, the drug was administered intravenously. Two of these had the dilatation reduced, while in the third it was prevented. Painting the superior mesenteric ganglion of a fourth cat prevented the dilatation of the intestine. We believe that we have proven that the mechanism causing vasodilatation in the intestine, when adrenalin is injected into the general circulation, is located in the collateral sympathetic ganglia, probably in the superior mesenteric ganglion.

Location of the Limb Mechanism

If the adrenalin vasodilator mechanism for the hind limb is not located in the brain or spinal cord, it must be located in some structure situated between the cord and the peripheral nerve trunk, either the ganglia of the sympathetic chain or else the ganglia of the dorsal roots. Judging from the location of the intestinal mechanism it would seem more logical that the sympathetic ganglia were the structures sought.

The right hind limb of a dog (26.0 kgm.) was placed in a plethysmograph. The last five lumbar and the first sacral sympathetic ganglia were destroyed on the right side. The limb was next com-

pletely shut off from the circulation and perfused with warm oxygenated Ringer's solution. Injection of 1.5 cc. of 1:20,000, adrenalin into the jugular vein caused slight dilatation of the perfused limb, while double the dose caused a marked dilatation.

A second animal was studied after destruction of the last five lumbar and the first two sacral sympathetic ganglia. The dilatation from adrenalin was very marked.

In a third dog both sympathetic chains were completely destroyed on both sides from the third lumbar ganglion downward. The perfused limb dilated as in the other experiments when adrenalin was injected into the general circulation.

The animals were always examined at the completion of the experiments to ascertain the limit of gangliar destruction.

We were first inclined to believe that the mechanism for the limb was not located in the sympathetic ganglia, but that it must be in the dorsal root ganglia. However this appeared to be wrong, as the following experiments indicate.

In two dogs we were able to obtain dilatation, in a perfused limb, from adrenalin injected into the jugular vein after all dorsal root ganglia to that limb had been destroyed.

In another experiment we destroyed the sympathetic ganglia on both sides beyond any region which might supply the limb used for perfusion. Good dilatations were obtained in the perfused limb. Then the spinal nerves were cut distal to the dorsal root ganglia. No response could be obtained. Therefore we were forced to the tentative conclusion that either

the dorsal root ganglia or the central nervous system was the seat of action after sympathetic destruction. But other experiments described above have shown that the central nervous system is not involved. Moreover we obtained dilatation in the perfused limb of a dog after the sympathetic ganglia and the dorsal and ventral roots central to the ganglia had been destroyed.

Thus far our work indicates that the limb mechanism is located in both the dorsal root ganglia and the sympathetic ganglia.

Comparison of the Two Mechanisms

Obviously, if there is to be a shifting of blood from the splanchnic area to the muscles the dilator mechanisms for the intestine and the limb must behave somewhat differently because the intestine contains a large share of the "splanchnic" blood. The two mechanisms do behave differently. While small doses of adrenalin produce constriction in the intestine and dilatation in the limb, larger doses cause constriction and dilatation in the intestine and constriction in the limb. Greatly increasing the dose above that causing intestinal dilatation does not cause predominant constriction in the intestine unless the mechanism has been fatigued by huge doses. In addition to these differences we have evidence that the limb mechanism is developed earlier than the intestinal mechanism.

Occurrence of Adrenalin Vasodilator Mechanisms

It might be said that these mechanisms may be of little importance because of the possibility of their being limited to the carnivora. We have been mak-

ing a survey of the vertebrates for this reason. Although it is not completed it will be of interest to note some of our results.

The mechanisms seem to be absent in the Reptiles (turtle), Birds (fowl) and at least one order of Mammals, viz., the Rodents (rat and rabbit). In view of their absence in the Rodents we were much surprised to find them present in a lower mammal, one of the Marsupials (opossum). It seems that they are found in all of the carnivores, at least those tried (cat, dog, ferret). We have shown, therefore, that these mechanisms are not limited to the carnivora.

Discussion

It begins to appear that both the dorsal root ganglia and the sympathetic ganglia contain vasodilator mechanisms which are susceptible to adrenalin. These mechanisms cause dilatation in the vessels of the limb and probably in the vessels of all skeletal muscle. The collateral sympathetic ganglia contain vasodilator mechanisms for the intestine, but whether the dorsal root ganglia contain similar mechanisms for the intestine we cannot say.

Of the two types, the skeletal muscle mechanism may be the more important because it causes shifting of the blood to parts that need it most in times of action. We can suggest no good reason for the existence of the intestinal mechanism unless it be to prepare a ready reservoir for the blood when the pressure increases, from too great a constriction of the vessels of other regions. Even though intestinal dilatation may begin with doses which are not pressor in their action, it might be preparing the

way for the return of the blood from the muscles with greater amounts of adrenalin. The very fact that the intestines continue to dilate with increasing doses of adrenalin although the muscle vessels reverse and begin to constrict lends color to this suggestion.

The picture which we have at present in regard to the action of adrenalin on the blood vessels is this:

A mammal at birth (excepting the rodents), responds to adrenalin by constriction of the vessels pretty generally over the body, i.e. both in the intestine and skeletal muscle, no matter how large or how small the dose if it is effective, so that only a rise in blood pressure can be obtained. After a few weeks, about eleven in the cat, the skeletal muscle mechanism begins to appear; adrenalin now causes a shifting of the blood to the muscles when entering the circulation in small quantities and a fall in blood pressure may result because of a predominance of dilatation over constriction. But it is somewhat later that increasing the dose of adrenalin will cause dilatation of the intestine although the limb vessels will reverse and constrict. And then finally we find developing the intestinal mechanism which can be brought into play with the larger amounts of adrenalin.

Recapitulating,—in the adult, adrenalin poured into the blood in small quantities, causes by its peripheral effects, constriction of the vessels in the skin, mucous membranes, and abdominal organs, driving the blood into the vessels supplying the skeletal muscles which are actively dilated for its reception through the effect on the sympathetic and dorsal root gangliar mechanisms. But as the quantity of adrena-

lin liberated increases, the peripheral effect begins to overcome the gangliar effect in skeletal muscle, the intestinal vessels by action on the sympathetic ganglia begin to dilate and the blood is reversed in its path.

Although the effect of adrenalin on blood pressure, a fall with small doses and a rise with larger doses—is the more evident, the differential effect is after all the more important.

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A NOTE ON THE USE OF CORPUS LUTEUM TO PREVENT THE PAINFUL BREASTS OF MENSTRUATION

By H. Lisser, A.B., M.D.

Instructor in Medicine, University of California Medical School

Coincident with the increasing interest in endocrinopathies there has come widespread development of organotherapy. Much has been accomplished; far more remains to be unraveled and properly evaluated. Probably we have barely scratched the surface in this promising sphere of therapeutics, but unfortunately a great deal of indiscriminate use of ductless gland extracts has ensued, much of which will be deservedly discarded.

At present, Corpus Luteum, is receiving much attention and many remarkable results have been claimed for it. It would seem to be of considerable value in ameliorating or even eliminating the disagreeable symptoms of the menopause; especially the artificial menopause. It has been recommended by one eminent authority as very useful in combating the vomiting of pregnancy, although some dispute this. It has been advocated in sterility, and in an occasional selected case may prove successful. Some authors have found it beneficial in functional amenorrhea; and also in dysmenorrhea. It has been tried in many other conditions, and in the course of time it will find its proper place in our therapeutic armamentarium.

All clinical experimentation on human beings is in the nature of things inaccurate, since it is difficult to control and is influenced by prejudice. The report of an isolated instance is of course, valueless,

but it would seem that the following case embodies a new observation, to which it may be worth while calling attention. So far as I am aware, Corpus Luteum has not been used to influence the painful breasts so common during menstruation or just previous to it. However, in the extensive literature bearing upon the ductless glands which has accumulated in recent years, I may have very well overlooked a report similar to my own. In most women the breasts are somewhat tender at this time, but in a small minority they become so acutely painful as to constitute a really distressing symptom, the relief of which is quite welcome.

The patient was a young married woman, aged 24, and came to me in January, 1916, with two complaints—obesity and very painful breasts at the menstrual period.

Family history. Her father died when patient was very young; he was not fat. Her mother has always been stout, but of late years very fat indeed, up to 260 pounds. She is slightly taller than the patient, who is five feet 2 inches. Patient is the only child living and the only child that came to term. There were premature twins born dead. The mother has three sisters and one brother; none of them are stout except the sister, who is very stout. The mother of the patient has taken Thyroid Extract and lost 80 pounds in three months. There is therefore, a family tendency to ductless gland disturbances.

History. Patient has been married 3½ years; never pregnant. Patient has always been well except for occasional tonsillitis (she has recently had tonsils removed). She is rather thirsty, drinks more water than normal and voids rather frequently. She perspires neither more nor less than normal. She is normally bright and active and is definitely not stupid or sleepy. Sexual intercourse is not gratifying.

Menstral history. Regular every 28 days; flows profusely; lasts 6 to 9 days; suffers considerable pain so that frequently she remains away from work (school teacher) for a day or two. Breasts are very painful 5-6 days before her periods, so painful that she can barely touch them or have her clothes come in contact with them.

Examination. Short stout girl, excellent complexion, color good; 5 ft. 2 inches; weight 2½ years ago, 160 pounds; average

weight, 145 pounds; weight on first visit to me, 140 pounds. Patient has a little more hair on lips, chin, and cheeks than normal, otherwise no abnormal distribution. Hands are short, wrists thick; relatively short forearm; round, fat face; fat, somewhat pendulous abdomen; thick, heavy hips; fat pads on upper chests, and large pendulous breasts. This abnormal fat is not painful. Tongue is not thick. Patient shows no signs of hyperthyroidism. Tonsils are enlarged. Eyes normal, mouth normal, thyroid normal, heart normal, lungs normal, abdomen normal, reflexes normal. Pelvis, normal (confirmed by competent gynecologist). Blood pressure, 125/95.

Treatment. From January, 1916 to June, 1916, patient was given thyroid extract (B. & W.) up to 15 grains per day without any ill effects. Her weight was reduced from 140-130 lbs., no success resulted from attempting to reduce it further by thyroid treatment.

During this time, as heretofore, she complained regularly of dysmenorrheoa and very painful breasts. Beginning with August, 1916, she was given Lutein tablets (H. W. & D.) 5 grain tablet t.i.d. The effect was prompt and remarkable. She was completely relieved of her painful periods and her breasts were perfectly comfortable; in fact, not tender at all; the periods did not last so long and the bleeding was not so profuse.

During the following months, sometimes by accident and sometimes purposely, Lutein Tablets were omitted and on each occasion she experienced a return of her painful periods and very tender breasts. Apparently, then, Lutein Tablets were not in any sense curative, but whenever taken prevented the disagreeable disturbances associated with menstruation. This is summarized as follows:

January, 1916—No Lutein. Much pain with periods. Very painful breasts.

February, 1916—No Lutein. Much pain with periods. Very painful breasts.

March, 1916—No Lutein. Much pain with periods. Very painful breasts.

April, 1916—No Lutein. Much paid with period. Very painful breasts.

June, 1916—No Lutein. Much pain with periods. Very painful breasts.

July, 1916—No Lutein. Much pain with periods. Very painful breasts.

August, 1916—Took Lutein. No pain with periods. No pain in breasts.

September, 1916—Took Lutein. No pain with periods. No pain in breasts.

October, 1916—Took Lutein. No pain with periods. No pain in breasts.

November, 1916—Took Lutein. No pain with periods. No pain in breasts.

December, 1916—No Lutein. Much pain with periods. Very painful breasts.

January, 1917—Took Lutein. No pain with periods. No pain in breasts.

February, 1917—Took Lutein. No pain with periods. No pain in breasts.

March, 1917—Took Lutein. No pain with periods. No pain in breasts.

April, 1917—No Lutein. Much pain with periods. Very painful breasts.

May, 1917—No Lutein. Much pain with periods. Very painful breasts.

June, 1917—No Lutein. Much pain with periods. Very painful breasts.

July, 1917—Took Lutein. No pain with periods. No pain in breasts.

August, 1917—No Lutein. Some pain with periods. Breasts very sore.

September, 1917—No Lutein. Some pain with periods. Breasts very sore.

October, 1917—Took Lutein. No pain with periods. No pain in breasts.

November, 1917—Took Lutein. No pain with periods. No pain in breasts.

Conclusion. Case is reported in which Corpus Luteum entirely relieved unusually painful breasts associated with menstruation. This would seem to be a new observation.

A favorable effect was had as well upon the dysmenorrhea and menorrhagia.

A STUDY OF THE SYMPTOMS OF EXOPHTHALMIC GOITRE

By Francis M. Pottenger, A.M., M.D., LL.D.,
Monrovia, Cal.

In my work as a specialist in tuberculosis, I have been impressed with the frequency with which we find enlargement of the thyroid gland in the early active stage of the pulmonary form of this disease. In fact, it is not infrequently that the diagnosis of exophthalmic goitre instead of tuberculosis, is made in these cases on the three symptoms: enlargement of the thyroid, acceleration of the heart beat, and loss of weight. Although the eye symptoms are not present, it is explained on the basis of the diagnosis being made before the complete syndrome has manifested itself.

Since becoming interested in the subject of visceral neurology, I have been impressed with the unsatisfactory explanations which have been offered to account for the clinical phenomena which accompany this disease. While many phases of this clinical picture must, with present knowledge, continue to remain doubtful, there are certain physiological and anatomical relationships whose discussion may serve to clarify some of the troublesome points. In this paper I do not desire to express dogmatic opinions, but rather to discuss relationships which may be suggestive and helpful, approaching the subject mainly from the interesting viewpoint of visceral neurology.

Graves' Disease presents a picture, the complexity of which has not been sufficiently appreciated, partly because the subject has been approached

from too narrow a standpoint. Attention has been centered too much on the prominent symptoms and not enough upon the other phases of the disease. Among the various standpoints from which it will bear discussion, are:

1. The vegetative nervous system,
   (a) sympathetic,
   (b) parasympathetic.
2. The central nervous system.
3. The various glands of internal secretion.

THE RELATIONSHIP TO THE VEGETATIVE NERVOUS SYSTEM

I.

Sympathetic Nervous System

It is important to note that three of the cardinal symptoms of this disease: exophthalmos, increased thyroid secretion and rapid heart, are manifestations of irritation of sympathetic fibres. The rapid heart, and possibly the thyroid secretion and the eye symptoms, may be caused by general sympathetic stimulation; but all could be accounted for by a stimulation of the *cervical* sympathetics without a general sympathetic stimulation. It is important then to determine whether or not there is an irritation in the cervical ganglia of the sympathetics in cases of Graves' Disease, or whether the motor cells in these ganglia are unduly sensitive to stimuli.

In recent studies by Wilson and Durante[1] and Wilson[2], important references to the literature on this subject are discussed in connection with their own valuable contribution to the subject. In the former paper they say:

"It would appear from our examination by the method detailed, that definite histologic changes do occur in the cervical sympathetic ganglia in hyperplastic toxic (exophthalmic) goitre."

and further:

"These histologic changes consist of various states of degeneration, viz (a) hyperchromatization, (b) hyperpigmentation, (c) chromatolysis, and (d) atrophy, or (e) granular degeneration of the nerve cells. All of these are but successive steps in degeneration, which, if uninterrupted, proceed to the complete destruction of the ganglion cells affected. Not all of the ganglion cells in any of the ganglia examined were so completely destroyed as to render improbable their return to normal under favorable conditions. There is some evidence that in ganglia from cases clinically improved some of the cells have partially or wholly recovered."

A stimulation which would be sufficient to cause degeneration of nerve cells, in all probability, would be preceded by a preliminary period in which the cells would be only in a state of increased excitability.

This calls for an examination into the relationship which the cervical sympathetic ganglia bear to the eye, the thyroid and the heart; and an especial discussion of the question whether the changes in the cervical ganglia produce the thyroid stimulation or whether the changes in the thyroid cause the irritation and, later, degeneration in the ganglia and are indirectly responsible for the heart and eye symptoms.

Anatomical Consideration. The cervical ganglia send off the following branches of particular interest in our discussion:

1. *Eye.* Motor fibres to the Müllerian muscle and dilator fibres to the pupil. Found only in the superior cervical ganglion.

2. *Thyroid.* Efferent cells to this gland are found in both the superior and medium cervical ganglia.

3. *Heart.* The motor cells which send accelerator fibres to the heart are found in the superior, medium and inferior cervical ganglia, the latter being the chief source.

From anatomical considerations then, an irritation of the superior cervical ganglion might stimulate efferent cells which would, reflexly:

1. Cause a shortening of the muscle of Müller which pushes the eyeball forward, causing exophthalmos.

2. Stimulate the thyroid gland to increased secretion and, if excessive, produce hyperthyroidism.

3. Stimulate the accelerator fibres going to the heart, causing the rapid heart found in this disease. (There are also other causes operative in Graves' Disease which tend to cause rapidity of the heart as will be mentioned later).

The experiments of Cannon, Binger and Fitz[3] support the foregoing conclusions.

Stimulation of motor cells in the medium ganglion might affect fibres going to the thyroid and the heart; and stimulation of the cells of the inferior ganglion would affect the heart alone, but very strongly.

Physiological Considerations. In order to discuss the question of the relationship of the changes in the cervical ganglia to the thyroid gland, we must discuss one of the fundamental and most important principles involved in studying the vegetative nervous system, viz: *When the various ganglia of the sympathetic system migrated from the central nervous system, did they carry with them the powers of the cells in the gray matter of the central system to mediate reflex acts?*

This is a most important question from the standpoint of physiology. Such able students of physiology of the vegetative nervous system as Langley[4] and Gaskell[5] believe that reflexes do not take place through sympathetic afferent neurons and efferent motor neurons except as contact is had in the cord. They thus deny the possibility of a reflex taking place from one viscus to another, the synapse occurring in sympathetic ganglia. On the other hand, Bechterew[6] quotes approvingly the work of Ramon Y. Cajal, who believes that a reflex may be formed between sensory sympathetic and motor sympathetic

neurons in sympathetic ganglia; the cells of the ganglia having the same function as to the production of reflexes as those of the central nervous system from which they migrated.

Thus it will be seen that if the view held by the English physiologists is correct, it is impossible for afferent impulses traveling centralward from a toxic goitre to produce histological changes in the cells of the cervical sympathetic ganglia, such as have been described by Wilson and Durante, because the nutrient cells of the afferent neuron lie in the ganglion of the posterior root. On the other hand, if the view of the continental physiologists is correct, this is possible, for nutrient cells of the sensory neurons would also be found in the cervical ganglia. We are now face to face with a situation in which clinical pathology may be able to settle the discussion upon this important physiological principle. *If it can be shown that the pathological changes in the cervical sympathetic ganglia are secondary to the prolonged irritating afferent impulses which come from a pathological thyroid, and that exophthalmos and rapid heart are reflexly caused by the ganglionic changes, then it is established as a fact that the cells in the sympathetic ganglia possess the power to mediate reflexes.* Further investigation along this line is most desirable. The important experiments carried out in Cannon's laboratory do not throw light on this question, because the union is with the preganglionic fibres.

Three Views of Graves' Disease from Its Relationship to the Sympathetic Nervous System

From our discussion so far and that which follows, we are led to see that as far as the cardinal symptoms, exophthalmos, hyperthyroidism and

tachycardia, are concerned, Graves' Disease might be any one of the following:

1. *A disease produced by certain pathological conditions in the sympathetic nervous system, which show as increased excitability with lowering of the threshold of response in selective portions of the system, affecting particularly neurons which go to the eye, thyroid and heart.*

2. *A disease of the sympathetic ganglia, in which a chronic irritation, affecting the ganglion cells which give origin to fibres supplying the muscle of Mueller, the thyroid gland and the heart, is present.* This, in the superior cervical ganglion, could affect the motor cells to all of these organs; if in the medium, to the thyroid and heart; and if in the inferior, to the heart alone.

3. *A disease of the thyroid gland which causes afferent impulses to travel centralwards to the cells in the cervical sympathetic ganglia, and on account of their persistency produce chronic stimulation which later results in histologic change.* Resulting from this stimulation there takes place a persistent activation of the motor cells which innervate the muscle of Müller, resulting in protrusion of the eyeball; and of those which innervate the heart, resulting in tachycardia. (This can only occur if sympathetic ganglion cells have the power of mediating reflexes).

Aside from the cardinal symptoms above mentioned, which are distinctly of sympathetic origin, there are a few cases in which the entire disease picture is that of a lessened vagus or a positive sympathetic irritation, as mentioned by Eppinger and Hess[7]. Such cases have excessive tachycardia; no sweating; no marked gastrointestinal symptoms;

slight rise of temperature; no eosinophilia; and at times, alimentary glycosuria. Such cases must not necessarily be considered as being due alone to the action of the thyroid secretion upon the sympathetic nerves. In this connection we must consider that the sympathetics and parasympathetics in their opposition to each other do not always exert an equal force. It seems to me possible that some of these cases are those in which the stimulation of the parasympathetics is not wholly able to overcome the normally high (for the individual) sympathetic tonus. This will be discussed in relation to "vagotonia" later. Owing to the reciprocal relationship generally admitted to exist between the thyroid and adrenals, the sympathicotropic action of adrenalin must play a part in every clinical picture.

Circulatory Phenomena. The circulatory phenomena are intensely interesting. The heart beat is accelerated, and strong, often so strong that it causes an uncomfortable pulsation in the larger vessels, such as the aorta and carotids. This at times causes a shaking of the head and marked pulsation of the abdominal aorta. Contrary to the increased muscular tonus of the heart and large arteries, the walls of the peripheral vessels are relaxed, as is shown in the flushing of such peripheral structures as the face, ear and fingers.

This condition in the vascular system argues in favor of the cause of the tachycardia, being in the sympathetic ganglia which give off motor fibres to the heart. The blood vessels of the head, neck and upper extremities receive their constricting sympathetic fibres from connector neurons originating from the I to the X, particularly the II, III and IV thoracic

segments of the cord (Gaskell) and the motor cells supplying the vessels are found in all of the ganglia connected with this part of the cord. The heart itself receives accelerator fibres from motor cells in the superior, medium and inferior cervical ganglia; and an irritation of the motor cells in these ganglia for the heart, might take place without causing general stimulation of the motor fibres going to the vessels supplied by neurons which are connected with the same thoracic segments.

We can not, however, look upon the tachycardia which accompanies this disease as being so simple in explanation as that of a stimulation of some of the accelerator neurons in the cervical ganglia. Much of it must be accounted for by the stimulation of the adrenals and the general increase in metabolic activity, while part of it is of central origin. Neither must the psychical state of the patient be omitted from consideration in accounting for it.

II.

Parasympathetic Nervous System

While the cardinal symptoms above described are manifestations of increased stimulation on the part of the sympathetic nervous system, there are many other symptoms which show distinct evidence of parasympathetic stimulation. When we consider the full symptomatology of this disease, we are forced to the conclusion that it is of such a nature that its symptoms are not due to effects exerted on the vegetative system alone, nor on one division to the exclusion of the other, but to many causes, including disturbances in the central nervous system, in psychical equilibrium, and in the equilibrium of the endocrine glands.

Many of the common symptoms, however, belong to the group which represents stimulation of the parasympathetics, thus:

1. *Von Graefe's Sign.* When eyes are lowered the upper lids do not follow the cornea readily, because of the high tonus in the musculus levator palpebrae, innervated by the III nerve.

2. *Dalrymple's Sign.* Widening of the lid slits, giving the expression of fright is due to the same high tonus in the musculus levator palpebrae.

3. *Epiphora.* Increase in flow of tears, due to stimulation of the vegetative fibers of the VII nerve.

4. *Excessive Sweating.* Sweating from the manner in which it is influenced by pilocarpin, atropin, and adrenalin, seems to be due to parasympathetic stimulation. This, however, is not certain.

5. *Diarrhoea.* Diarrhoea is produced by an excessive stimulation of the glands and longitudinal muscles of the gut; and since all of the muscles of the gastrointestinal tract are activated by the parasympathetic (vagus and pelvic) nerves, this must be considered as parasympathetic stimulation.

6. *Hyperacidity.* This is evidence of an increased action on the part of the secreting glands of the gastric mucosa which are innervated by the vagus.

7. *Eosinophilia.* This blood picture seems to predominate in states which accompany a predominant stimulation of the parasympathetic system.

With reference to the non-cardinal symptoms, it must be remembered that they are not constant. Some of them, like diarrhoea, are found in 30 per cent of cases (Sattler), vomiting in 15 per cent; while the metabolic disturbances which must be looked

upon as the most important pathological change in this disease, were found, according to Kocher, in 88 per cent of all cases examined by him.

Considering the vegetative system alone, it is evident that Graves' Disease is accompanied by both sympathetic and parasympathetic symptoms; and if we account for all as being due to thyroid secretion, it must be a complex polyvalent substance (Biedl.[8]) It seems to me equally plausible that thyroid secretion, in its sensitizing role, lowers the threshold of response, and that the group of symptoms which presents depends: (1) upon the constitutional underlying tonus (sympathicotonia or vagotonia); and (2) upon the tonus of individual organs in the same individual, and the manner in which the nerve cells respond to stimuli.

RELATIONSHIP TO THE CENTRAL NERVOUS SYSTEM

Neurasthenia, and mental disturbances, are common in this disease.

Tremor is exceedingly common, and is thought by many to be of central origin. It is most marked in the upper extremities. It is to be looked upon as being evidence of increased irritability of motor centers.

There seems to be a general disturbance in the equilibrium of nerve cells of such a nature that the threshold of response for stimulation is lowered. This manifests itself in a general unsteadiness of many body functions.

In many cases, such centers as the vasomotor, respiratory and vomiting are disturbed.

Psychical disturbances of all grades are found during the course of the disease.

RELATIONSHIP TO OTHER ENDOCRINE GLANDS

The secretion of the thyroid gland is one of the most important chemical regulators of the body, and one without which the patient can not long exist. Further, because of its action upon other important structures, and its interrelation with other glands of internal secretion, when produced in overabundance, it will disturb functions which depend on a normal balance of secretion from other important glands of internal secretion. The precise relationship which exists can not be stated no matter how essential to this present discussion. Suffice it to say that the entire equilibrium in the chemical, as in the nervous control of the body, is disturbed and often destroyed when the secretion of the thyroid gland is either markedly increased or decreased. Particularly is there reciprocal relationship supposed to exist between the thyroid and the adrenals, pancreas, thymus, and gonads. The relationship of the thyroid to these structures will be further discussed in this paper in relationship to Kendall's interesting reports.

Influence of Vagotonic and Sympathicotonic Dispositions Upon Symptomatology

The conception of an underlying vagotonic and sympathicotonic constitutional disposition, as suggested by Eppinger and Hess[7], is of great importance to clinicians in helping to explain the variability of symptoms as they exist in medical practice. All the smooth muscle and all secretory glands of the gastrointestinal tract and all the structures which have been formed embryologically from it, such as the respiratory and part of the genitourinary tract, and

the liver and pancreas as well as other glands of internal secretion, are supplied by fibres from both the sympathetic and parasympathetic systems. In each instance one system activates and the other inhibits; and equilibrium of action or normal function is maintained by the effects of the two systems balancing each other. This equilibrium under normal conditions is fairly stable. A considerable stimulation on the part of either system may be withstood by the opposing nerves without normal function being disturbed. There are some structures also which are innervated wholly by one of the systems alone. There are a great many individuals, however, in whom the tonus of one or the other of these systems is commonly above normal. If the tonus in the sympathetic system is stronger than normal, then a slight increase of sympathetic stimulation may cause marked sympathetic symptoms. Such a person is normally sympathicotonic. If the parasympathetic tonus under normal conditions is abnormally high, then a slight increased stimulation of parasympathetic fibres may produce marked parasympathetic symptoms. Such a person is normally vagotonic.

The natural underlying disposition is often sufficient to modify greatly or even determine the character of the symptoms; and it is well to bear this in mind in analyzing the symptoms of any disease, but particularly in one such as Graves' Disease, in which all nerve activity is heightened.

Eppinger and Hess divide Graves' Disease according to whether the symptoms are predominantly those of sympathetic or parasympathetic stimulation, into sympathicotonic and vagotonic types, thus:

Characteristics of the *Vagotonic Type* are: 1, relatively slight increase in pulse rate; 2, subjective cardiac symptoms; 3, marked von Graefe's sign; 4, wide lid slits; 5, very moderate exophthalmos; 6, marked epiphora; 7, excessive sweating; 8, profuse diarrhoea; 9, gastric hyperacidity; 10, eosinophilia; 11, disturbance in respiratory rhythm, and 12, absence of alimentary glycosuria.

Characteristic of the *Sympathicotonic Type* are: 1, marked exophthalmos; 2, epinephrin mydriasis; 3, Moebius' sign; 4, frequently dry eye; 5, a high degree of tachycardia without subjective cardiac symptoms; 6, no sweating; 7, no diarrhoea; 8, falling out of hair; 9, rise in temperature; 10, absence of eosinophilia, and 11, alimentary glycosuria.

In these two types of Graves' Disease it should be noted that the *vagotonic* type shows a general widespread parasympathetic stimulation, while the *sympathicotonic* type shows most marked symptoms on that part of the sympathetic system whose motor cells lie in the cervical ganglia. The two noticeable exceptions to the last statement are, slight rise in temperature and alimentary glycosuria, which, if due to sympathetic stimulation or increased adrenal secretion, are a result of general and not local action. The adrenals are stimulated by thyroid secretion.

The rise of temperature can easily be accounted for by the increased metabolism which is present, especially if associated with vasomotor disturbances which interfere with heat dissipation. In this connection it has been estimated (Barker)[9] that an individual at rest with a well marked hyperthyroidism utilizes as much oxygen as a man at hard work. Not only is nitrogenous metabolism accelerated, but car-

bohydrate and mineral as well. In severe cases CO_2 production and O_2 consumption may increase 70 per cent (Falta)[10]. Cannon's[3] experimental animals increased as much as 150 per cent.

Alimentary glycosuria is supposed to be due to increased stimulation of the adrenals, caused by the increased thyroid secretion. Gley[11] does not accept this relationship with the adrenals as established. Kendall, however, believes it an essential part of thyroid activity. Since alimentary glycosuria is not regularly found in this disease, it might be looked upon as due to some peculiarity of the patient or to some general condition which exists, and not necessarily an integral part of the syndrome of hyperthyroidism.

DISCUSSION

In studies of visceral neurology and endocrinology, it is essential to be familiar with the tendency which such and such nerve stimulation or such and such chemical products from endocrine glands has to affect certain actions; but the analyst must not be unmindful of the fact that the physiological organism is exceedingly complex and that definite tendencies may be altered or wholly controverted; otherwise, the more independent physiological facts which are at his disposal, the greater his confusion.

In the light of the above analysis, it seems not improbable that we have been confusing several different conditions in our picture of Graves' Disease, thus:

1. A local sympathetic stimulation confined to the motor cells of the cervical ganglia, which may be primary and cause the sympathetic eye symptoms, being a factor in the production of tachycardia and causing

the hypersecretion of the thyroid, this gland being activated by the sympathetics, as shown by Cannon and Cattell[12]; or a local stimulation of the cells of the cervical sympathetic ganglia which results from irritating afferent impulses from the pathological thyroid gland forming synapses in the cervical ganglia and reflexly influencing the eye and the heart.

2. Changes in metabolism and disturbances in physiological equilibrium throughout the organism which are directly and indirectly due to a hypersecretion of the thyroid gland, most of which changes seems to be of a vagotonic nature.

3. A variable symptomatology due to: (a) natural underlying constitutional tendencies, such as sympathicotonia and vagotonia; (b) to variability in tonus of the nerve supply to different organs in the same individual, and (c) to differences in secretion from various endocrine glands.

Both the local sympathetic stimulation and general parasympathetic (vagal) stimulation is well illustrated in the eye. The muscle of Müller, which is activated by the sympathetics and unopposed by vagal fibres, is contracted and causes protrusion of the eye ball. This is made permanent by a deposit of tissue posteriorly to the ball after it is forced forward by the muscle. The levator palpebrae which is activated by the III nerve (parasympathetic) and unopposed by the sympathetic, causes widening of the lid-slits, and Von Graefe's sign. These are sometimes present but often absent, depending on the strength of the vagal stimulation. The pupil which is dilated by the sympathetic and contracted by the parasympathetic fibres in the III nerve, sometimes shows the effect of stimulation of one system, some-

times of the other, depending on whether the tonus in the one or the other system predominates. Dilated pupil is not constant like the exophthalmos, although it results from stimulation affecting motor cells of the sympathetics in the same ganglion. The difference might be accounted for in that the sympathetic stimulation of the muscle of Müller is unopposed, while that of the pupil is opposed by the III nerve.

The very interesting experiments of Cannon[3] must not be overlooked, for they show that a chronic irritation of the cervical sympathetics may produce an artificial condition not unlike exophthalmic goitre. He anastomosed the phrenic nerve in cats with the cervical sympathetics which supply the thyroid. After the animals had fully recovered from the operation and union of the nerves had taken place, a condition was present in which a stimulation of the cervical sympathetics occurred with each respiratory excursion. These animals developed exophthalmos, tachycardia, diarrhoea, greatly increased metabolic activity, and while in the dark a rythmic contraction and dilatation of the pupil with each respiratory movement. Cannon believes that exophthalmic goitre may be of central origin and that it occurs in individuals in whom the threshold of response in the sympathetic nerve cells supplying the organs involved is lowered so as to allow impulses to pass with unusual ease.

It might add further light to our discussion to include cases of hyperthyroidism, which are not accompanied by exophthalmos. There seem to be two predominant etiological factors in hyperthyroidism: One, deep emotions, sexual excitement and fear; the other, such infections as those of the nasal sinuses

and tonsils, alveolor abscesses and pulmonary tuberculosis.

While chronic infections of other structures such as the digestive tract and urogenital tract, as mentioned by Barker may be etiological factors, it will be noticed that infections commonly recognized as producing hyperthyroidism are confined to structures of the head and chest, structures which receive their sympathetic innervation from the upper six thoracic segments of the cord and which further return their afferent impulses through the cervical sympathetic ganglia. It would be well to bear this in mind for future study in order to determine if possible whether reflexes are taking place in these ganglia which result in stimulation of thyroid activity. McCarrison[13] claims that intestinal toxemia is most commonly followed by hyperthyroidism. Toxemias act particularly through the sympathetics, as do such emotional states as are instrumental in producing hyperthyroidism; but this action seems to be general and would probably require some particular underlying cause on the part of the thyroid gland itself, in order to have an increased secretion on its part dominate the sympathetic picture.

Experimental attempts to produce exophthalmos by the use of thyroid feeding are interesting. The reports seem to be decidedly conflicting, and it can be said that true exophthalmos has so far not been readily produced. Falta[10] quotes the experiments of Kiam and Friedental and Hönnicke, as being successful through the administration of large quantities of thyroidin. He says they induced both a widening of the palpebral fissure and an exophthalmos, although not of a very marked degree. This seems

to be a physiological paradox, for widening of the palpebral fissure is due to parasympathetic stimulation through the III cranial nerve, while exophthalmos is due to sympathetic stimulation. If both of these effects result from the thyroidin, it seems most probable that one may be a direct action, while the other must be indirect and probably produced by some other chemical substance resulting from the stimulation of other endocrine glands, or that the thyroidin contains more than one active substance.

The secretion of the thyroid gland stimulates the adrenal glands, which are sympathicotropic. It might do this either as a part of a general sympathetic stimulation ,or as a selective chemical stimulation confined to the gland itself. It has also been stated that thyroid extracts sensitize the nerve terminations on which adrenalin acts (Levy[14]). Paton[15] quotes the work of Asher and Rodt as showing the effect of blood containing the products of the thyroid gland when injected into animals. Inasmuch as the thyroid secretion stimulates the action of the adrenals, they treated the blood with formaldehyde, which destroys the adrenalin "and found that the serum injected in a series of cases caused increased vagus excitability, increased action of adrenalin and increased irritability of the splanchnic and of the depressor nerve."

Hoskins[16], in an interesting editorial (Endocrinology, Vol. 1, 1917, p. 404) on this subject supplies the experimental proof from his own work as well as that of others to show that there is a strong interrelationship between the secretion of the thyroid and adrenals.

It would thus look as though thyroid secretion is a sensitizer of nerve cells. This phase has been particularly emphasized by Crile[17]. It would further seem that it has the property of activating both the sympathetic and parasympathetic systems. This from the knowledge of other physiological substances, seems hardly probable as far as the same substance is concerned; for these two groups of neurons are antagonistic in action wherever found. Does it not seem more probable that the thyroid secretion lowers the threshold of response in nerve cells generally; and in its action upon nerve structures, acts either as sympathicotropic or vagotropic, more probably the latter; and that aside from those symptoms which might result from irritation in definite ganglia, such as the cervical, the sympathicotonic symptoms which manifest themselves might result from the increased adrenal secretion, another thyroid product, or a particular sensitization of certain tissues acted upon by adrenin? This, if we accept thyroidin as being vagotropic (Gley[11]), would lead us to consider a vagotropic substance as acting upon the adrenals, which otherwise are stimulated by sympathetic irritation; or, compel us to assume that there are other substances in the thyroid secretion than the thyroidin which acts upon the adrenals. We must remember, however, that the chemical control of the body is lower in the course of development than the nervous system, and it is possible that some such a reciprocal relationship was necessary in order to maintain equilibrium. As it is necessary to make flexor muscles taut in order to maintain an equilibrium when extensors are contracting, so it might be necessary for a gland which

secretes a vagotropic substance to stimulate another gland to secrete a sympathicotropic substance in order to maintain an equilibrium in those functions presided over by hormones.

While the prominent symptoms, exophthalmos and tachycardia, may be results of sympathetic stimulation, we are not warranted in assuming that they necessarily result from the action of thyroid secretion upon the sympathetic cells which innervate them. These symptoms and the increased thyroid secretion itself may be due to common sympathetic stimulation.

The striking feature of thyroid hyperactivity is its influence upon metabolism; the speeding up of metabolic changes resulting in the rapid breaking down of protein and only a slightly lower destruction of carbohydrates. Since the musculature and secreting cells of the entire gastrointestinal canal and the organs derived from it are innervated by the parasympathetics, it would seem that the action of thyroid secretion upon metabolism must be vagotropic as far as it acts upon vegetative structures; but since the increase in metabolism extends likewise to voluntary structures, we must not take too narrow a view of its action. Kendall[18] reports the function of the thyroid. He says:

> "While it has not been proved beyond controversy, there is much evidence to support the hypothesis that the function of the thyroid is to furnish the animal organism with ammonia resulting from the diaminization of amino-acids. The amino-group in amino-acids is unavailable for the formation of urea and other nitrogenous compounds until it has been split out of the amino-acid. This diaminization seems to be the function of the thyroid."

The other ductless glands, such as adrenals, pancreas, parathyroid and thymus, in the opinion of

Kendall, are also concerned in the conversion of nitrogen compounds into their proper end products. He says further:

"The thyroid hormone is involved in the first split of ammonia from the amino acids. The adrenal cortex secretion then converts this substance into some other and the secretions of the thymus, the parathyroids, and other ductless glands are involved in the further elaboration of the nitrogen constituents which finally appear in the urine. It, therefore, is evident that the administration of the thyroid hormone merely starts an increased rate of production of ammonia, which, in itself, does not produce hyperthyroid symptoms. It is only when the other ductless glands are stimulated that the reaction is carried on at a rate sufficient to change the basal metabolism, the irritability of the nerves, and the other effects produced by administration of the thyroid hormone. These reactions take place within the tissues and, in part, within the blood; and the speed with which they occur, and hence the equilibrium maintained, producing an increase or decrease in metabolism, depend on the stimulation of the various endocrine glands and the ability of the tissues to carry on the reactions which are made possible by the secretions from the various glands."

The work of Kendall is of great importance and confirms the idea that we are attempting to account for too many of the conditions which manifest themselves in Graves' Disease, as being directly due to the thyroid secretion. The disease is extremely complex; and while the hypersecretion of the thyroid gland starts the picture, it does not end until other ductless glands, the voluntary and vegetative nervous systems, the circulatory and digestive systems, and the entire metabolism, are severely deranged.

SUMMARY

1. Exophthalmic goitre is an extremely complex picture in which the clinicians have emphasized too much the exophthalmos, tachycardia and enlarged thyroid; while the real picture is that of a rapidly destructive metabolism dependent apparently upon the thyroid hypersecretion and its influence on the

nervous system and on other endocrine glands.

2. The relationship of the three prominent symptoms, exophthalmos, tachycardia and thyroid hyperactivity is not clear. These may all be evidence of the same stimulation of the cervical sympathetics; or the thyroid gland may be diseased primarily and the afferent impulses from it so irritate the nerve cells of the cervical sympathetic ganglia as to cause the marked stimulation of those motor neurons which supply the muscle of Müller and the heart, and cause exophthalmos and tachycardia.

3. If exophthalmos and tachycardia result from stimuli which emanate from the diseased thyroid, the synapse in all probability occurs in the cervical sympathetic ganglia, and the reflex would be proof that sympathetic ganglion cells have the reflex properties of the cells of the central nervous system.

4. Omitting the three localized cervical sympathetic symptoms, exophthalmos, enlarged and functionally hyperactive thyroid, and tachycardia; and the increased activity of the adrenals; most of the common visceral symptoms of this disease seem to manifest themselves in parasympathetic rather than sympathetic stimulation.

5. The variability of the symptoms seems to depend on the sensitizing influence of thyroid secretion upon nerve cells, lowering the threshold of response to nerve stimulation on the one hand, and to the natural underlying, predisposing nerve tonus as described by the terms sympathicotonic and vagotonic by Eppinger and Hess, and the relative tonus of these two divisions of the vegetative system in different organs of the same individual.

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COMMENT ON DR. POTTENGER'S ARTICLE

Swale Vincent, M. D., University of Manitoba, Winnipeg: Dr. Pottenger's paper would form a good introduction to a discussion on the whole subject of Graves' Disease and the physiology and pathology of the thyroid gland. The reader will be impressed by the amount of thought and ingenuity which has been

expended upon the subject; although, it must be confessed, the amount of actual original observation seems to be very small, amounting in fact to the record of frequent thyroid enlargement in the early stages of pulmonary tuberculosis.

One of the most interesting questions from a general physiological standpoint raised by Dr. Pottenger is that which concerns reflex action from the sympathetic ganglia. Langley and Gaskell are quoted as representatives of English physiologists who are opposed to the view that such reflexes are possible. I imagine that the list of English physiologists who are of this opinion might be considerably extended. Moreover, it may be questioned whether it is permissible to quote the views of Bechterew on this point as typical of those of "continental physiologists." I have carried out no investigations on the subject, but for teaching purposes I have assumed for some years that the matter was practically settled and that the verdict was against the occurrence of sympathetic reflexes. Certainly Dr. Pottenger has not adduced sufficient fresh evidence to disturb my belief.

As for the share played by "vagotonia" and "sympathicotonia" in the symptom-complex of Graves' Disease, it would be well to exercise due caution in expressing any opinion until such time as a sufficient amount of clinical evidence has been accumulated. It is at any rate consoling that Dr. Pottenger says nothing about "Hormone X."

AN ENDOCRINE PROBLEM

Recent experimental evidence is concordant in indicating that the secretion of adrenin is neither essential to life nor, under ordinary conditions, particularly significant as a factor in the physiologic economy. On the other hand clinicians, and particularly, certain of the French, continue to maintain that as a therapeutic agent adrenin even in very small doses is often effective. Milian, for example, claims that it is almost a specific against the alarming symptoms that occasionally attend the use of salvarsan. Even allowing for the potency of therapeutic suggestion, the persistence of such claims stands as a challenge to those who believe in the relative inefficacy of adrenin.

No thoughtful experimentalist will maintain that current laboratory methods of endocrine research are sufficiently delicate for the satisfactory investigation of many problems. At best merely tentative conclusions can be drawn from various laboratory experiments in this field.

Much more delicate are the spontaneous experiments which come under the eyes of clinical observers. But unfortunately in such experiments the conditions are usually beyond control and the analysis of the phenomena observed highly difficult. Moreover, the mental attitude, the preconceptions and tendency to theorize, upon the part of many clinical endocrinologists militates against a proper objective treatment of such data.

In an article abstracted in this number of Endocrinology Tracy has stated that a few drops of

adrenin a day administered subcutaneously or even placed under the tongue cause a marked augmentation of the vasoconstrictor reaction to stroking the skin. The writer has observed a small dose of adrenin hypodermatically to cause a marked generalized itching in a patient with an unstable vasomotor system.

In view of the admitted inadequacy of the methods hitherto employed an attempt to develop a more delicate technique for the investigation of adrenin problems has been made in the physiological laboratory of the Northwestern University Medical School, using the vasomotor reactions in animals without anesthesia, the operating and recording being carried out under local narcosis. Allowing, however, for the sensitizing effect of cocaine employed in the earlier experiments, no significant differences were detected between the reactions of anesthetized and non-anesthetized dogs.

Possibly Tracy's observation could be made the basis of an experimental technique, using either human or animal subjects. Also Cannon's observation that the denervated heart of an otherwise normal animal is very sensitive to adrenin might possibly be utilized. Other methods might be evolved which would obviate the necessity for anesthesia or immediate trauma.

If so, the whole problem of the pharmacology of adrenin could profitably be re-investigated. Similarly the influence of many factors such as hyperthyroidism and hypothyroidism upon the adrenin reactions should be further studied. Thus various clinical findings and experimental observations might be brought into closer harmony.

ENDOCRINOLOGIA—PATOLOGIA E CLINICA. By Professor N. Pende. 1916, Pp. 1034, with 147 illustrations. Milan, Vallardi. Lire 35.00.

Prof. Pende's book is much more than a learned compilation of what was known about Endocrinology at the time of its publication. It is a successful effort toward a well balanced systematization where his deep knowledge of the new science is rendered even more interesting by the author's many original and nearly always genial views. Moreover the development is well ordered and the attempt is made to avoid any conclusion not based on well established facts.

The author emphasizes the hormonic action of the endocrine system in the three fields, "neuro-regulator, chemo-regulator and morpho-regulator." Although he believes that the study should comprehend also certain non-endocrine glands Pende deems it necessary, owing to the uncertainties of the new science, to keep within the limits of the purely endocrine system.

Each gland is to be considered potentially able to produce hormones of different qualities, the action of which would not be simultaneous but determined by the needs of the tissues or of the organs. The action of the hormones may be either direct on the cells or mediated through the nervous system.

According to the author there is no such thing as an "anti-toxic action" of the endocrine glands,—understood as a neutralizing action of the hormones on endogenous or exogenous toxins. The effect is obtained through their influence on the metabolism, which may either evoke antibodies from other tissues (bone marrow, lymphoid organs) or stimulate the activity of eliminative organs (liver, kidneys, etc.).

As to direct antagonism between hormones of different glands and their occasional vicarious func-

tion the author is rather skeptical, as he thinks that their action is exclusively determined by the need of the tissues or of the organs. In this way every change of activity on the part of one forces the other endocrine glands to adapt their own activities to the new exigencies created in the organism.

The book includes an intricate diagram illustrating Pende's hypothesis of an endocrine-sympathetic balance, based on a distinction between the "vegetative" and the "animal" systems. There is a certain degree of independence between the two systems; moreover their growth is not simultaneous, but alternating in such a way that, while one grows, it seems to hinder the growth of the other. According as one or the other predominates there may be two distinct types of development: i.e. the *Microsplanic* for the animal life and the *Macrosplanic* when the vegetative life prevails. Some hormones belong either wholly or partially to the one and some to the other system. The functional harmony of the individual organism depends on the balanced functioning of the two hormonic categories.

Intraglandular Hormones—The plurality of different hormones in the same gland is demonstrated for many of them; and the author feels justified in assuming such plurality for all glands in explanation of the apparently contradictory effects which the same gland may produce in the organism.

Endocrine-Sympathetic Relations—Seeing that these two systems are related reciprocally and that their functions are perfectly analogous Pende makes one system of both and calls it the "Endocrine-sympathetic system." Their synergy is shown by the reciprocal action of diseased conditions of either one on the other, and by nervous heredity on the genesis of endocrine diseases, as well as by the influence of glandular heredity on the genesis of sympathetic diseases.

Physio-Pathology of the Genital Internal Secretion—The genital internal secretion is produced by the testis and the ovary; but very likely there is some endocrine activity in the prostate, the mamma and the uterus, also. Besides the endocrine activity of their epithelial elements it seems that the connective tissue may assume the appearance and function of secreting elements, as in case of the myometral gland of the rabbit and by the interstitial cells of the testis and the ovary.

The interstitial glands appear early in the testis, before any differentiation of sex, and their greater development in the foetus is indicative of a future male development. There seems to be an inverse relation between the growth of the tubular and interstitial tissues, as one is hypoplastic when the other is in full activity.

As for the ovary, though the cells from the epithelial tissue as well as those derived from the connective tissue are both "luteinic cells," the lipoids and functions of the interstitial cells cannot substitute the lipoids and functions of the corpus luteum.

The action of the genital hormones is more decided in conditions of genital insufficiency than in normal conditions. This is to be understood as regards their general action. As for their action on the development of the genital organs they do not determine the sex which is a matter of heredity, but only help to accentuate the differentiation of the sexes. The other hormones (thyroid, hypophysis) do not have any such differentiating action.

Besides the action on the development of the sexual characters the genital hormones influence the development of the skeleton, stimulate the general metabolism and, partially, the nervous system.

Physio-Pathology of the Adrenal System and of the Para-Sympathetic Organs—Pende emphasizes the probable significance of the union of the cortex and the medulla of the Adrenals and claims that

there must be some necessary interrelation of action between the two systems. The connection of the two elements becomes closer the more perfected the organism.

The *carotid gland* is only partially of cromaffine tissue; the coccigeal gland does not belong to the cromaffine system.

The author does not admit that the phenomena of sympathetic stimulation, due to fear or anger, are effects alone of adrenal hypersecretion; other glands may concur in this (thyroid).

It is very difficult to judge the action of adrenin from the large doses used in experiments. As for the relation of adrenin to the genesis of atheroma Pende believes that in most of cases it is due to other causes, seeing that the type of the lesion is different. He believes that the accessory cortical tissue and the parasympathetic cromaffine tissue are not able to function adequately in place of the cortex and the medulla of the adrenals. The syndrome of medullary insufficiency is not due merely to deficiency of adrenin in the blood.

Hypophysis and Pineal Gland—The difference between the colloid substance of the prehypophysis and of the neuro-hypophysis is emphasized. The pharyngeal hypophysis is constant in man and is analogous but not identical in its structure with the anterior hypophysis. The lack of differentiation of its tissue and its lack of reaction to changes in the organism, while the anterior hypophysis reacts, demonstrate its minor importance.

The author found in pregnant cats signs of hyperfunction of the anterior hypophysis in the formation of the "gravidic cells" which are never found in the non-gravid hypophysis. They occupy a great part of the tissue of the gland. Pende noted also a hypertrophy of the paraneural layer during pregnancy.

The author considers the *Pineal* an endocrine gland. It is connected by means of medullated nerve

fibres with the diencephalon and with the mesencephalon. As for its secretion there has been found an amorphous transparent substance, grains of a yellow pigment and lipoid granules(?). Besides the hormone action on the organism, some local action through its nervous elements is regarded as probable. Pende calls it a "neuro-glandule," to be classified with the hypophysis and the para-sympathetic glands.

Thyroid—The colloid substance passes into the lymphatics; this *mobilization* seems to be aided or inhibited by physiologic factors which would act, like those mobilizing the glycogen from the liver, according to the needs of the organism. The excessive accumulation of colloid in the vesicles while there are signs of atrophy or inaction of the epithelial cells shows inactivity and not hyperactivty of the gland. A hyperfunctioning thyroid may be poor in colloids since it is sending them promptly into the circulation. The presence of solid, undifferentiated thyroid epithelium shows hyperfunction. The foetal thyroid is active, though it does not show all the elements found in the thyroid. The thyroid has not only an action on catabolism but also on anabolism.

After removal of the thyroid the growth of the body is not so much hindered as is the growth of the limbs: i. e. the growth of the animal system is more retarded than that of the vegetative system. According to the author the influence of the thyroid is rather on the morphologic evolution of the organism than on the general growth.

The action of the autonomic system (Langley) on the thyroid is twofold. Activity of the para-sympathetic innervation leads to the accumulation of the secretion within the gland; if, on the other hand, the sympathetic is dominating there is more activity and more prompt mobilization of secretion.

Parathyroids—The importance of the parathyroid lipoids is emphasized. The colloid is like that

of the hypophysis and is eliminated through the blood vessels. It has nothing in common with the thyroid colloid.

In cachexia parathyreopriva, when the removed glands have been grafted successfully so that the condition develops very slowly there is no spasmophilia.

The removal of the parathyroids creates instability of the thyroid function.

The symptoms caused by the removal of the thymus may be like those of parathyroid deficiency owing to certain functions shared between the two glands, but the function of the one cannot replace the function of the other.

Thymus—We must admit as secreting elements: the lymphocytoid cells, the epithelioid cells of the medulla with their hypertrophic forms, the corpuscles of Hassall and, finally, some peculiar eosinophil elements always present in the periods of activity of the organ.

The pathologic synergy of the thymus with the hemo-lymphopoietic organs is explained by the presence of many more lympho-adenoid and myeloadenoid elements than in any other endocrine gland.

Pancreas—The author believes that both the tissues, the acinar and the insular, concur in the pancreatic secretion, and that, in pathologic conditions, the one may take the place of the other.

CLINICAL ASPECTS OF THE ENDOCRINE ORGANS

After a thorough semeiologic introduction the author suggests the following diagrams for the puriglandular syndromes and for the monoglandular syndromes.

PLURIGLANDULAR ENDOCRINE SYNDROMES

I—Pluriglandular syndromes with dominating uniglandular syndrome (with form of myxoedema, exophthalmic goitre, acromegaly, etc.)

II—Pluriglandular syndromes given by association of various monoglandular syndromes (myxoedema plus acromegaly plus Addison's disease).

III—Attenuated pluriglandular syndromes, whose type cannot be defined (many of Lorain's infantilisms, some cases of feminism, of attenuated virilism, of neuro-arthritic syndromes, etc.)

IV—Endo-exocrine pluriglandular syndromes (association of hepatic or renal cirrhosis with endocrine syndromes as Basedow's, Addison's diseases).

SUGGESTED CLINICO-PATHOLOGIC CLASSIFICATION OF THE MONO-GLANDULAR ENDOCRINE SYNDROMES.

I—Thyroid—

Athyroidism—Complete myxoedema of adults, Bourneville's myxoedema.

Hypothyroidism—Incomplete myxoedema of adults, infantile incomplete myx-idiocy, paroxistic hypothyroidism, hypothyroidism minimus, mono-symptomatic hypothyroidism.

Hyperthyroidism
- Harmonic (orthoplastic)—hyprthyr. constitution, pubertal crises, menstrual crises, temporary emotional hyperthyr.
- Disharmonic (metaplastic — Basedow's syndrome (classic), partial Basedow syndromes, thyroid instability.

II—Parathyroid—

Aparathyroidism—Severe tetany, spontaneous or post-operative.

Hypoparathyroidism—Slight tetany, spasmophilia.

III—Pituitary—

Apituitarism—Cachexia hypophyseopriva, pathologic lethargy.

Hypopituitarism—Froehlic's distrophy adiposo—genitalis, nanism, hypophyseal infantilism, hypophyseal feminism.

Hyperpituitarism
- Harmonic (orthoplastic)—euritmic gigantism, hyperpituitarism of puberty and of pregnancy.
- Disharmonic (metaplastic) — acromegaly, hypophyseal gigantism and acromegalogigantism.

IV—Adrenal—

Asuprarenalism—Asuprarenalism acute, with sudden death, choleriform, apoplectiform, pseudo-peritonitic, myocardic, encephalitic.

Hyposuprarenalism—Syndrome of Addison, periodic asthenia, gravidic hyposuprarenalism, etc.

Hypersuprarenalism
- Harmonic (orthoplastic)—athletic constitution, and hypertonia.
- Disharmonic (metaplastic)
  - cortex — pseudohermaphroditism, hermaphroditism of suprarenal origin, virilism, precocious macro-genitosomia.
  - medulla — hypertensive crises, temporary glycosurias, arterio-necroses.

V—Genital—

Agenitalism—Syndrome from early castration, syndrome from late castration.

Hypogenitalism—Eunucoidism (geroderma) eunucoid feminism, late hypogenitalism, virilism of ovarian origin, genital obesity.

Hypergenitalism
- Disharmonic (metaplastic)—Precocious puberty of primitive genital origin with heterosexual symptoms, Chlorosis?
- Harmonic (orthoplastic)—hypergenital constitution, euritmic precocious puberty, hypergenital nanism.

VI—Thymic—

Athymism—Severe congenital idiocy(?)

Hypothymism—Pedatrophy with atrophy and softness of the bones and muscular atrophies(?)

Hyperthymism
- Harmonic (orthoplastic) — Infantile macrosomia(?)
- Disharmonic (metaplastic) — Status thymicus of young and adults.

VII—Pancreatic—

Apancreatism—Severe lean diabetes.

Hypopancreatism—Slight fat diabetes, alimentary glycosuria, pancreatic obesity.

VIII—Pineal—

Apinealism—Macrogenitosomia precox of pineal origin pineal cachexia, pineal obesity.

—Giuseppe Vercellini.

ABSTRACTS

1. (ADRENAL) Capsules surrénales et allaitement. (Suprarenal capsules and lactation.) Verdozzi, (C.) Arch. Ital. de Biol. (Pisa) 1917, **66,** 121.

The author has studied the changes in the adrenal glands during pregnancy and the following period of lactation in the guinea pig. Animals weighing between 400 and 600 gms. were used. As a basis for comparison, the adrenals of a series of adult virgin females were employed. In these the relation of adrenal to body-weight varied from 1:1000 to 1:1350.

The period of gestation was estimated by the weight and length of the foetus. Twenty-four animals constituted the series in this phase. There was a marked increase in the weight of the adrenals due to hypertrophy of the cortical substance. If, following birth, the guinea pig was hindered from suckling its young, the weight of the adrenal capsules, which, at the moment of birth, was generally higher than the normal weight, diminished rapidly and descended below the average normal figure. If, on the contrary, the guinea-pigs were permitted to suckle their young, the weight of the adrenals increased rapidly, attaining the maximum at the end of about fifteen days. In the latter case it was the cortex which hypertrophied, especially the fasciculated and reticulated zones, the lipoid and pigments increasing.

Because the cortical adrenal substance is developed early in the embryo and increases in volume and apparent activity after birth, especially in the state of gestation, and during nursing, Verdozzi believes that the adrenal cortex is an important factor in the development and general nutrition of the organism.—F. A. H.

2. (ADRENALS) The function of the suprarenal glands. Tieken (T.) Med. and Surg. (St. Louis) 1918, **2,** 18-25.
(From Rush Medical College, Chicago.)

A brief historical discussion of the subject with a summary of the author's views as to the present status of the adrenal problem.—R. G. H.

3. (ADRENALS) A note on some obvious consequences of the high rate of blood flow through the adrenals. Stewart (G. N.) Am. Jour. Physiol. (Balt.) 1917, **45,** 92.

"From the relatively great quantity of blood passing through the adrenals, it might be expected that the blood of the adrenal veins would differ less from arterial blood than does ordinary veinous blood." Calculation shows that the adrenal vein blood would contain only 1 cc of oxygen per 100 cc of blood less than arterial blood. "Yet a recent writer (Menten; abstracted in this Journal) thinks it worth while to demonstrate that the oxyhemoglobin bands in adrenal vein blood" are stronger than those in jugular vein blood from the same animal.

For the same reason the author takes exception to the statement of Menten and Crile that the increased alkalinity of the adrenal vein blood is due to its adrenalin content. The great flow through the adrenals results in a greater alkalinity than in mixed veinous blood; it acquires less CO_2 and is nearer to arterial blood. "It is not easy to gather in what way these writers suppose that the changes in the reaction of the adrenal vein blood is produced by the adrenalin in it."—T. C. B.

4. **(ADRENALS) Uber die diagnostischen Verwendung von Adrenalin besonden bei Milztumoren.** Oehme (C) Deutsches Arch. Klin. Med. (Leipzig) 1917, **122,** 101.

The lymphocytosis caused by adrenin is not a reaction only of the lymphoid tissue in the spleen, but of the lymphoid system generally, especially in the abdomen; the action of vegetative nerves also plays a part, the contraction of smooth muscle forcing the cells into the blood stream. The diminution in size of the spleen which occurs after adrenin is of diagnostic value in tumors of left hypochondrium.—Physiol. Abst.

5. **(ADRENIN) Die Beziehung der Nebennieren zur Piqure.** Biberfeld (J) Arch. exp. Path. Pharm. (Leipzig) 1916, **70,** 164.

In rabbits diuresis occurred, but there was no effect on carbohydrate metabolism either on piqure or on injection of adrenin.—Physiol. Abst.

6. **(ADRENIN) Uber den Adrenalingehalt der Nebenniere des Menschen.** Lucksch (F.) Virchow's Archiv. (Berlin) 1917, **223,** 290.

The total amount of adrenin in both adrenals is about 8 mgs. or 4 mgs. per gram of gland. Various diseases lower this, especially infectious diseases; the smallest quantity found was in Addison's disease, the largest in nephritis.—Physiol. Abst.

7. **ADRENIN. Vasodilator mechanisms in the cat at different ages.** Hartman (F.) and Kilborn (L. G.) Am. Jour. Physiol. (Balt.), 1918, **45,** 111.

The authors accidentally discovered that adrenalin in any dose fails to cause a fall in blood pressure in kittens. The only reaction is a rise. "As the fall in blood pressure is controlled by a central nervous mechanism, the failure of this mechanism to develop at an early age might account for the reaction in young kittens."

The results of observations on young kittens may be summarized as follows: The smallest effective dose of adrenalin causes a rise of pressure in young kittens, and the threshold is high. The response by a fall of pressure begins at about eleven weeks, and the mechanism is gradually developed. The fall of blood pressure is due to vasodilitation in the muscles. The intestinal dilator mechanism often develops later than the limb mechanism, thus supporting the view that the two mechanisms are different. (See also "Adrenalin Vasodilator Mechanisms," Hartman, in this issue.)—T. C. B.

8. **ADRENIN, Some actions of, upon the liver.** Bainbridge (F. A.) and Trevan (J. W.) Jour. Physiol. (Lond.), 1917, **51,** 460.

The authors have already shown that a slowly continuous injection of adrenin causes obstruction of the blood flow through the liver, and if the obstruction is prolonged the animal passes into a condition of shock. The present paper gives the methods employed, and describes the immediate effects of adrenin upon the blood flow in the liver.

The partial pressure was recorded from the splenic vein and the vena cava pressure from the illiac vein. The recording manometer was filled with 3.5% solution of sodium citrate.

When adrenin is injected either into a systemic vein or into a radicle of the portal vein, there is a rise of portal pressure, increase of the volume of the liver, and an increased flow of lymph from the thoracic duct. There is little or no alteration in the vena cava pressure. These effects are due to some obstruction of the blood flow from the liver, caused by the adrenin.

From theoretical considerations, as well as from the results of injecting distilled water, the authors think the obstruction may be due to a "narrowing of the capillary channels by swelling of the columns of liver cells, although the evidence does not warrant a definite conclusion."—T. C. B.

9. **(ADRENIN) Beiträge zur Physiologie der Drüsen, Leon Asher.** XXVII. Untersuchungen über die Automatie des Schleiendarmes und deren Beeinflussung durch Adrenalin. Backman (E. L.) Ztschr. f. Biol. (München) (1917) **67,** 307.

In experiments with the isolated intestine of the fresh-water fish Cyprinus tinea, automatic movements were maintained for an hour in oxygenated Tyrode's solution of half the usual calcium content. Large slow contraction lasting several minutes and a smaller series were observed. Pure adrenin 1:20,000,000 had an inhibiting effect on the automatic movements. In the preparation hemostasin, however, weak concentrations stimulated the contractions owing to the presence of chloretone, inhibition occurring with higher concentrations. Pilocarpine augmented the tonus and contractions of the intestine. The fish intestine is presumably provided with a sympathetic inhibiting and parasympathetic augmenting, nervous mechanism. Adrenin does not affect the muscular contractions produced by direct electrical stimulation.—Physiol. Abst.

10. (ADRENIN) Neosalvarsanexanthem und Adrenalinwirkung. (Exanthema caused by neosalvarsan and the influence of adrenin.) Nageli (O.) Cor.-Bl. f. schweiz. Aertze (Basel), 1917, **47**, 1291.

A very remarkable case is described. A patient, fifteen minutes after an injection of 150 mgs. of neosalvarsan developed an exanthema. Twenty minutes later this exanthema had disappeared. Each time after injection of neosalvarsan the exanthema reappeared.

If, however, adrenin was injected first and some minutes later the injection of neosalvarsan was given, no cutaneous reaction was observed. The dose of adrenin required to prevent the reaction depended upon the dose of neosalvarsan; 0.5 mgs. adrenin was enough to prevent it when 300 mgs. neosalvarsan was injected. When, however, 600 mgs. neosalvarsan was injected it was necessary to inject one mg. of adrenin to avoid the exanthema.—J. K.

11 (ADRENIN) The alleged relation of the epinephrin secretion of the adrenals to certain experimental hyperglycemias. Stewart (G. N.) and Rogoff (J. M.) Am. Jour. Physiol. (Balt.) 1917, **44**, 543.

The view has been expressed that perhaps most of the forms of experimental hyperglycemia (asphyxia, piqure, etc.) are dependent primarily upon excitation of the adrenals to increased secretion of epinephrin, thereby mobilizing the sugar, as does adrenalin when artificially introduced. The fact that subsutaneous injections are more effective is against this idea, and the experimental basis for these conclusions is quite unsatisfactory, for they are made on dying animals (practically) due to the removal of the adrenals, or on animals suffering from a major operation and anesthesia.

The relation of epinephrin secretion to hyperglycemia can be better investigated by the method of removing one adrenal and sectioning the nerves of the other. In this way the secretion is abolished, while the animals remain indefinitely in good health.

Using this method it is found that hyperglycemia associated with asphyxia or anesthesia can be obtained just as well as in cats that have not undergone the operation. There seems to be no essential difference between operated and control animals.

Observations on "emotional hyperglycemia" do not support the view that this condition is a constant or even a common phenomenon in cats.—T. C. B.

12. (ADRENIN) Studien über antagonistische Nerven. XIII. Die Wirkung des Adrenalins auf die Gefässe der Niert des Frosches und die Veränderungfähigkeit dieser Wirkung. Zuckerstein (S.) Ztschr. f. Biol. (München) (1917) **67**, 293.

In eleven experiments in which the glomerular capillaries of the frog's kidneys were perfused by methods used in Asher's laboratory, via one of the aortic arches, with hemostasin and Ringer's solution, the drop number diminished from 74 to 45 per cent. By the substitution of physiological salt for Ringer's solution, i.e., in the absence of calcium—the constricting effect of adrenin was abolished or much diminished. A repetition of these experiments on the tubular capillaries of the kidney perfused via the posterior vena cava was entirely negative, although the vessels responded to barium chloride by vigorous contraction. The failure of these vessels to react with adrenin points to the absence of sympathetic innervation. After complete section of all the visceral nerves in three frogs, adrenin caused dilatation of the glomerular vessels, although barium chloride still caused constriction. Presumably adrenin acts on the neuroplastic end organs, which exhibit unusual conditions of excitation in early nerve degeneration. The results confirm the findings of Roy Pearce in another vascular area of the frog.—Physiol. Abst.

13. (ADRENIN) L'hyperglycémie et la glycosuri adrénaliques. (Hyperglycaemia and adrenalin glycosuria.) Phocas (A.) C. R. Soc. de Biol. (Paris) 1917, **80**, 938.

Adrenalin hyperglycaemia can be produced in rabbits deprived of their glycogen by fasting. Phocas suggests as an explanation of this the action of hepatic diastases upon substances other than glycogen (lipoids, glycoproteids) resulting in the formation of glucose. He assumes that adrenalin increases the quantity of hepatic diastases.

He determined the urea and phosphates of the urine of two starving rabbits before and after adrenalin injection. He found these notably increased on the second day after the injection, when the sugar disappeared from the urine. He believes that the glucose came from a large molecule, the nitrogen and phosphorus of which was excreted only after a final elaboration.—F. A. H.

14. (CORPUS LUTEUM) The existence of a typical oestrus cycle in the guinea pig with a study of its histological and physiological changes. Stockard (C. R.) and Papanicolaou (G. N.) Am. Jour. Anat. (Phila.) 1917, **22,** 225.

The authors have found from daily examination of the vagina of living animals and from microscopical studies that the guinea-pig has a regular dioestrus cycle lasting twenty-four hours and occurring every sixteen days. They conclude that the corpus luteum has a protective influence over the mucosa of the uterus and vagina since there is a parallel degeneration and development in all three organs. Ovulation was found to occur during every heat period. Absence of corpora lutea permits degeneration of the uterine epithelium.—E. R. H.

15. DIABETES INSIPIDUS, Maranon (G.) Siglo Médico (Madrid) 1917, **64,** 36.

The study of three cases confirms the modern view of the importance of the pituitary body in the genesis of diabetes insipidus. In one boy of three years of age, diabetes insipidus developed a few days after he had been shot in the head, the bullet lodging in the sella turcica and blocking the egress of the pituitary secretion. Treatment with pituitary extract alone relieved the symptoms.—Physiol. Abst.

16. DIABETES INSIPIDUS. Neue Theorie des Diabetes Insipidus (A new theory of diabetes insipidus.) Grundmann, Berl. klin. Wchnschr. (Berlin) 1917, **No. 31.**

The cause of diabetes insipidus is, according to Grundmann, very complicated. The author found symptoms of vagotonia and of a paralyzed sympathetic system. To understand the whole complex of symptoms it is necessary to believe in an abnormality of the endoerine system. The function of the hypophysis is increased, as is also the internal secretion of the pancreas. These hormones produce an increase of the function of the adrenals and of the thyroid gland. Therefore a therapeutic agent consisting of hypophysis extract alone cannot relieve these cases.

The theory of Grundmann, "increased adrenal function with a paralyzed sympathic system," sounds a little bit too theoretical. If this theory were right hypophysis extract alone would increase the symptoms; clinical experience has led to an opposite conclusion.—J. K.

17. **ENDOCRINE GLANDS, Studies on. I. The relation between the pancreas and thyroid and parathyroid glands. II. The relation of the pituitary body with the thyroid and parathyroid and certain other endocrine organs in the rat. III. The effects on the thyroid and parathyroid of the rat of administering thyroid extract and certain other autacoids and salts. IV. The effects in the dog upon the remainder of the thyroid and parathyroid of partial removal of those organs. V. Effects upon metabolism of castration, of thyroidectomy, of parathyroidectomy, and of thyroid and parathyroid feeding.** Kojima (M.) Quart. Jour. Exp. Physiol. (Lond.) 1917, **11**, 255-351.

A series of papers dealing with the effects of extracts of certain endocrine glands upon other organs. The point of view is largely histological.

The first paper deals with changes produced in the pancreas by feeding thyroid and parathyroid. After a week of thyroid feeding the pancreas of the rat shows typical changes; the alveoli are smaller, the alveolar cells are smaller, the nuclei vary in size and staining capacity, the cytoplasm of the cells contain comparative little zymogen, and there are many mitotic figures, indicating rapid multiplication. After an intermission in the thyroid feeding these changes disappear.

The addition of small ox-parathyroid to the daily diet causes no marked changes in the pancreas. In all the experiments the islets of Langerhans were unaltered. There are no differences due to sex.

A second thyroid feeding following the first after an interval seems to have less effect than the first.

After feeding for some time (about a month), mitoses are no longer seen, and the zymogen granules are again plentiful. The cells are still vacuolated.

The effects produced by feeding thyroid gland are also observed after administering water-extracts, both unboiled and boiled, and after giving the residue from these extracts. Alcohol and ether extracts have no effect, but the residue causes changes similar to those obtained by feeding thyroid.

Castration appears to have no effect upon the structure of the pancreas nor to influence the effect of feeding thyroid.

An artificial combination of iodine with protein has no effect. Of the various salts of iodine, the sodium salts seem

to produce the most marked effect, the most interesting change being the production of mitosis in the alveolar cells. This effect is not obtained when the rats have been previously thyroidectomised; the effect is probably an excitation of the gland. The effects due to pilocarpine, adrenalin, pituitary body, known to be glandular excitants are different. The original paper should be consulted.

The mouse gives similar results to the rat, but in the cat, dog, rabbit, guinea pig and bird, mitoses have not been seen. There is, however, a disappearance of zymogen granules from the alveolar cells.

The second paper deals with the effects on the pituitary of thyroidectomy, parathyroidectomy both complete and partial, and of castration.

Thyroidectomy causes the appearance of a number of large swollen cells in the pars anterior. To a less extent this is true of parathyroidectomy. Castration also has the same effect. The paper should be read for detailed descriptions of the histological appearances.

The third paper discusses the effects on the thyroid and parathyroids of administering thyroid extract and other autacoids* and salts. Administration of thyroid and of sodium and potassium iodides causes an accumulation of colloid in the vesicles of the thyroid of the rat. The cells of the parathyroids are generally swollen. Posterior lobe of the pituitary causes a swollen, barrel-like appearance of the epithelial cells of the thyroid. The structure of the parathyroids becomes loose. The cells are swollen and the nuclei shrunken. Adrenalin causes somewhat similar changes.

The fourth paper gives the microscopic appearances of the thyroid and parathyroids after partial thyroid and parathyroidectomy. The remaining portion of the thyroid undergoes proliferation of its epithelial cells, and the vesicles show marked polymorphism. There is little or no change in the parathyroids.

The effects of the thyroid and parathyroids, and of castration upon metabolism, are described in the fifth paper. Thyroidectomy in rats produces a dimunition of both nitrogen and calcium output.

After parathyroidectomy in rats there seems to be an increase of calcium in the urine, and less is retained in the body, but nitrogenous metabolism shows no definite change.

Thyroid feeding produces a decrease in body weight and a diminution of nitrogen and gaseous metabolism in all animals, whether normal, thyroidectomised, or parathyroidectomised.

*Schaefer's term for stimulating hormones.

Castration is attended in male rats by diminution of CO_2 output.—T. C. B.

18. ENDOCRINE organs in dementia praecox. Kojima (M.) Proc. Roy. Soc. Med. (Lond.) 1917, **10**, 88.

The thyroid tends to hypofunction in the male and to hyperfunction in the female. The sexual glands and adrenals are small in the female. The testes show only slight spermatogenesis. In the male the parathyroids contain clear watery cells and a few eosinophil cells; in the female the latter are abundant.—Physiol. Abst.

19. (ENDOCRINE ORGANS) Beziehungen zwischen endokrinem System und Konstitution. (Relation between the endoctrine organs and constitution.) Hart (C.) Berl. klin. Wchnschr. (Berlin) 1917, **54**, 1077.

Contains nothing new.—J. K.

20. (ENDOCRINE GLANDS) Le alterazioni delle ghiandole endocrine (specie del timo) e del sangue in seguito alla vagotomia. (The alteration in the endocrine glands [especially the thymus] and in the blood following vagotomy.) Pighini (C.) Patologica (Genova) n. 180, 1916.

The author of this experimental work comes to the following conclusions:

1. Chickens may live four-five days or more after the vagotomy; guinea pigs no more than four hours.

2. Among the effects of the vagotomy we must distinguish those due to the alterations of the respiration and of the circulation from those due to the lack of influence of such nerve on certain glands or systems.

Hypophysis, thyroid, the cromaffin tissue show hyperfunction. The thymus and spleen show atrophic conditions (especially the thymus of the chicken, which undergoes lipoid degeneration, seen also in the cortex of adrenals, ovary and testis and marrow of long bones).

There is also to be found a greater number of neutrophiles and lymphocytes, while the eosinophils are diminished.

3. The thymus, spleen, cortex of adrenals, interstitial cells of the testis and ovary and bone marrow have their internal secretion under the control of the vagus.

4. Hence by suppressing the vagi there is a predominance of the sympathetic system, demonstrated by the hyperactivity of the cromaffin tissue, thyroid and hypophysis and by increase of adrenalin in the blood. (S. Maggiore in La Pediatria, Jan., 1917.)—G. V.

21. ENDOCRINOLOGY, clinical, in general practice. Harrower (H. R.) Med. and Surg. (St. Louis) 1918, **2**, 41.

This article presents two outstanding features—an emphasis of the importance of endocrine disorders in every-day practice, and some dubious endocrine theorizing. As examples of such may be mentioned the statements that the adrenals control the action of the sympathetic system, that a continued state of "hyperadrenia" is possible (it would involve intestinal paralysis) and that adrenal exhaustion is frequently the final cause of death in severe infections. The article as a whole, in common with much of the endocrine literature, includes an amount of "explaining," which engenders a distrust of the subject matter itself.—R. G. H.

22. GAUCHER'S DISEASE. A report of two cases in infants. Knox (J. H. M., Jr.), Wahl (H. R.) and Schmeisser (H.C.) Bull. Johns Hop. Hosp. (Balt.), 1916, **27**, 1.

The paper opens with an analysis of the symptoms and findings in 16 cases of Gaucher's disease reported up to 1916. This is followed by a report of the cases of two infants, sisters, who did not thrive from birth and died, one at 11 months, the other at 15 months of age, from gradually increasing weakness. The striking clinical feature was the great enlargement of the spleen and liver. The blood picture showed moderate anemia. The leucocytes were rarely increased, and for the most part were markedly reduced in number. The skin in both cases had a peculiar yellowish-brown hue, more marked on the exposed surfaces. Microscopically, in both cases nearly all the organs were found to contain large, pale, granular or finely vacuolated cells, in which there was a peculiar refractive substance having the chemical and staining properties of lipoid material. Because of these findings the authors conclude that their two cases represent true specimens of Gaucher's disease.

The author's cases demonstrated a unique implication of the medulla of the adrenal glands, that the Peyer's patches and thymus were equally involved and that there was a general and diffuse distribution of the characteristic large cells; probably a manifestation of one and the same process, which in infancy is apt to be more rapid and widespread.

The conclusion is drawn that there is no evidence that the large pale cells characteristic of the disease are derived from any one particular tissue cell, but rather that different tissues may produce the same type of cell. It is primarily the endothelial cells lining the small lymph sinuses and the cells of the reticulum that become transformed into these characteristic large vaculated cells, and of these (author's cases) the rec-

ticular cells of the lymph-adenoid tissue appeared the most susceptible. Hence it would appear that Gaucher's disease is not primarily a disease of the spleen or of any other organ or set of organs, but is a generalized process due to a disturbance in fat metabolism, manifesting itself by a more or less diffuse accumulation of lipoid material in many cells, especially those of the hematopoietic system, with the formation of characteristic large pale cells.—H. W.

23. GAUCHER'S DISEASE, the cases of. Reported by Drs. Knox, Wahl and Schmeisser. Mandelbaum (F. S.) and Downey (H). Bull. Johns Hopkins Hosp. (Balt.), 1916, **27,** 109.

The article is a critical review of the two cases reported by Drs. Knox, Wahl and Schmeisser in the Johns Hopkins Hospital Bulletin, 1916, **27,** 1—abstracted elsewhere. From a careful consideration of the report and a thorough study of materials sent them by Dr. Wahl they conclude that the cells found and described by Drs. Knox, Wahl and Schmeisser are not the characteristic cells of Gaucher's disease, either as to their origin, structures or staining powers but rather represented typical cells found in cases of lipoidemia. After giving the origin, structure and staining power of characteristic cells found in cases of Gaucher's disease and comparing them with the two cases under consideration and certain other cases they state: "That a widespread cellular hyperplasia associated with degenerative changes in many organs, exists, is not denied, but we do insist that the cases are not to be classified with a well recognized disease, definite in its clinical manifestations and always accompanied by characteristic changes in a specific group of cells."—H. W.

24. (GOITER). Warnung vor Thymol bei Kropfkranken (Warning against Thymol in cases of goitre). Edens (E) Med. Klinik (Berlin), 1917, **13,** 807.

Edens saw two cases in which there was a goiter, which became toxic after the administration of thymol. In the first case the patient died, in the second one the patient recovered when she discontinued the use of a mouth water containing thymol.

Both patients were very nervous and lost weight as long as thymol was used.

Edens points out that the influence of thymol on experimental goiter was previously noted by McCarrison (Quart. Jour. Med., 1909).—J. K.

25. GROWTH. Patologia della crescenza (Pathology of growth). Marotta (A.). Libreria Detken (Napoli), 1914.

1. Diseases and abnormalities of the growing period are more numerous than is apparent.

2. They almost always occur between the ages of 2 and 16 years.

3. As predisposing conditions, heredity, urban life, insufficient food and unhygienic surrounding are important.

4. A very great influence is exerted by the endocrine glands.

5. The critical period is puberty. (S. DeStefano in La Pediatria, Feb., 1917.)—G. V.

26. (HORMONES). A bit of hormonology, with practical applications. Tracy (E. A.). Med. and Surg. (St. Louis), 1918, **2**, 35.

The article opens with the statement that "Epinephrin is a normal constituent of the blood." This is followed by a page of quotations from Falta of statements of various degrees of credibility which the author believes "clinicians will accept as presenting succinctly most of what is known of epinephrin activities." This belief the reviewer does not share.

Then follows an elaboration of a theory that the functioning of the autonomic nervous system is dependent upon and mediated through the presence of adrenin and pituitrin on the one hand and of thyroid, thymus and lymphoid tissue hormones on the other. For a discussion of the chief objections to this theory the reader is referred to Vincent's Critique on "Vagotonia" in the preceding number of "Endocrinology." One outstanding fallacy is the assumption that all vasoconstrictor fibers are sympathetic and all vasodilators, parasympathetic. The single fact that adrenin causes the capillaries of skelletal muscle to dilate serves to render the whole theory untenable.

The article further records some interesting observations upon the pharmacology of adrenin. It is stated that 1 to 3 drops of this substance placed under the tongue two or three times a day is sufficient materially to augment the cutaneous vasoconstrictor reflex to stroking.

The suggestion is offered that the sublingual route would be much more satisfactory for the administration of pituitrin in obstretrical practice than is the hypodermic route, since much better control would be possible.—R. G. H.

27. HYPERTHYROIDISM in the recruit. Brooks (H.) Jour. Am. Med. Assn. (Chgo.) 1918, **70**, 728.

(From Camp Upton Base Hospital.)

The author expresses surprise at the high incidence of hyperthyroidism among young male adults in the recruiting camps. The most prominent symptom is tachycardia, rarely

accompanied by arrhythmia. The rate is nearly always increased by exercise. Throbbing of superficial arteries is common, as is other evidence of cardio-vascular perturbation. The blood pressure is very low except in hypersensitive patients. Adrenin causes augmentation of the symptoms and there is an apparent hypersensitiveness to thyroid. Emotional instability is a very common manifestation.

In about two-thirds of the cases a definite hypertrophy or prominence of the thyroid is seen. Heredity plays a certain part in the syndrome. A considerable proportion of the subjects report a family history of goitre—usually maternal—and in most instances there is a family history of hysteria, insanity, perversions or genius. Exophthalmos is seen in the long-standing cases. In short, all the cardinal symptoms of exophthalmic goitre are present.

Many of the patients recover under the healthful and normal routine of camp life. Recreation and freedom from mental distress are important factors in recovery.—R. G. H.

28. (HYPOPHYSIS) The cell-changes in the hypophysis of the albino rat after castration. Addison (W. F. H.) Anat. Rec. (Phila.) 1917, **28,** 441.

Castration in the male rat is followed shortly by permanent alterations in the glandular portion of the hypophysis. There results a hypertrophy of the gland, an increase in the blood supply of the ventral lobe and an increase in the production of colloid. The basophiles and acidophiles of the ventral lobe which apparently are continually being differentiated from a common type of cell (reserve cell) that persists throughout life, are seriously affected, the former increasing in number and size, and undergoing vacuolar degeneration; the latter seemingly "de-differentiating" into reserve cells. The author regards the changes in the hypophysis as due to loss of the interstitial cells of the testis.—E. R. H.

29. (HYPOPHYSIS) Aus Hypophysengewebebestehender retropharyngealen Tumor. (A retropharyngeal tumor consisting of tissue showing the same structure as the pituitary body.) Leegaard (F.) Arch. f. Laryngol. (Berlin) 1917, **31,** No. 2.

Description of a case. The tumor was examined microscopically, and showed itself an adenoma. The author suggests the idea that these tumors can take their origin from little isles of tissue showing a pituitary structure. Normally such islands are always to be found in the wall of the pharynx. —J. K.

30. (HYPOPHYSIS) Case of dyspituitarism in a girl aged 15. Stephenson (S.) Brit. Jour. Chil. Dis. (Lond.) May, 1916.

A girl of fifteen offers simple bilateral optic atrophy, diminished power of vision of the left eye (5/36), sella turcica much greater than normal, absence of menstruation and of hair on the pubis. Given thyroidic therapy from 2 to 4 grm. a day, but without result. (From Abst. in La Pediatria, Feb. 1918.)—G. V.

31. (HYPOPHYSIS-DIABETES) Diabetes mellitus und acromegalie. Steiger, Ztschr. f. klin. Med. (Berlin) v. **74,** 324.

Steiger has observed five cases of acromegaly in two of which he found symptoms of diabetes. The combination of acromegaly and diabetes is not very rare. One of Steiger's patients died in diabetic coma; at the post mortem examination a tumor of the hypophysis and an increase of the connective tissue of the pancreas were found. The adrenals and the thymus were enlarged; there was a goitre and atrophy of the genitals.

Contrary to this there have been described cases of acromegaly and diabetes in which the pancreas showed a normal aspect. Therefore, Steiger concludes that it is incorrect to believe that the only cause of diabetes is an abnormality of the pancreas. Every disease he states, which disturbs the equilibrium of the endocrine system, may cause diabetes mellitus.—J. K.

32. (HYPOPHYSIS) The active principle of hypophyseal extracts. Houssay (B. A.) La Presna Med. (Buenos Aires) 1915, No. 5, p. 82. Correction, Endocrin. 1917, **1,** 393.

The active principle of the hypophysis is not by any known method obtainable pure and unaltered. The pharmacodynamic substance of hypophyseal extract is not the actual potent secretion.—B. A. H.

33. (INTERNAL SECRETION) A further contribution to the metamorphosis of Amphibian organs. The metamorphosis of grafted skin and eyes of Amblystoma punctatum. Uhlenhuth (E.) Jour. Exp. Zool. (Phila.) 1917, **24,** 237.

The author shows conclusively that two organs at least (skin and eye) are dependent for their full development upon some non-specific internal secretion which may be an agent like thyroid substance. In the experiments performed, pieces of skin and eyes of Amblystoma larvae were grafted onto larvae of the same and of other species. These grafts developed their own color markings but did this only if and when

the host metamorphosed, whether the host were younger or older than the animal from which the organs were taken.—E. R. H.

34. (INTERNAL SECRETIONS) Uremia and the internal secretions. Remond and Minvielle. Bull. Acad. Med. (Paris) 1917, **77**, 105.

Extracts of liver and thyroid were injected into animals; these bore the subsequent injection of human uremic serum better than controls did. The extracts also afforded a certain degree of protection against cantharides nephritis.—Physiol. Abst.

35. ORGAN EXTRACTS, effects of, on the contraction of voluntary muscle. Rogers (J.), Coombs (Helen C.) and Rahe (Jessie M.) Am. Jour. Physiol. (Balt.) 1918, **45**, 97.

A continuation of studies, some of which have been previously abstracted in this journal. This paper deals with the effect of the "residue" of various endocrine glands on striated muscle.

Residues from the thyroid, parathyroid and adrenal glands have the power of re-energizing fatigued muscle. Liver, spleen, ovary and pancreas do not have this effect, nor does the "coagulable" portion of the extracts of any of the glands.

Hypofunctioning of the thyroid and adrenals (and probably other endocrine organs) is accompanied by muscular weakness, and the authors think their results are significant from this point of view.

Excision of the thyroid seems to have no immediate effect upon the fatigability of striped muscle.—T. C. B.

36. (OVARY) Treatment of certain forms of asthma with ovarian substance and corpus luteum. Fishberg (M.) Med. and Surg. (St. Louis) 1918, **2**, 26.

(University and Bellevue Hospital Medical College.)

The article is an admirable variant from what we have learned to expect under such captions. After a brief discussion of possible endocrine factors in asthma, the author engagingly emphasizes the fact that in only a minority of his cases were favorable results obtained and that no adequate basis for theorizing is afforded.

Several illustrative cases are described.

The article concludes with a resumé: "Some cases of asthma in women are favorably influenced by ovarian therapy. In most of these cases there may be observed some relation between the asthmatic paroxyms and the generative functions. In some the attacks are ameliorated during preg-

nancy or menstruation; in others the paroxysms are more apt to occur, or are more severe when the patient is menstruating. In many cases of asthma occurring during the menopause, natural or artificial, the administration of ovarian substance relieves the dyspnea along with other symptoms of the menopause. Ovarian substance, or corpus leuteum, in moderate doses may, in these cases, act specifically, ameliorating the attacks or preventing their recurrence. Most of these patients seem to have a peculiar intolerance to the derivatives of opium which aggravate the asthmatic attacks and make them sick otherwise."

From the showing made in Fishberg's cases the treatment of asthma by ovarian substance would seem to be deserving of further critical study.—R. G. H.

37. (PARATHYROIDS) Tetany and the parathyroid glands. Koch (W. F.) Med. and Surg. (St. Louis) 1918, **2**, 9.

(From the Detroit College of Medicine and Surgery.)

This article is a discussion of the physiology of the parathyroid glands from a physico-chemical point of view. It begins with a section devoted to theoretical considerations which appeal to the reviewer as being, like many other physico-chemical discussions of biological topics, mostly an expanded paraphrase of admitted facts couched in an obstruse terminology.

Theoretical considerations aside, however, the article affords an admirable discussion of the present-day status of the parathyroid problem. It develops particularly a claim first put forward by Koch in 1913 that the essential feature of parathyroid deficiency is an intoxication due to the accumulation in the body of guanidin bases. Koch's findings have since been confirmed by Paton and his collaborators. On the basis of all available evidence it is maintained that the cause of parathyroid tetany is a guanidin intoxication of the central nervous system and the myoneural junctions.

A mother substance from which the guanidin may be formed is cyanamide, a body which may be recovered in methylated form from the urine of parathyroidectomized dogs. The cyanamide can readily take up ammonia to form guanidin. If not so converted to guanidin the cyanamide is readily hydrated to form innocuous urea.

Ammonia is normally excreted in combination with various acid radicals. According to Koch's view it is the route of disposal of ammonia, which is the determining feature in the causation of tetany. Anything which increases the acid content of the body would serve to deplete ammonia and hence decrease guanidin formation. The actual occurrence of tetany itself, by liberating lactic acid would thus tend to

check guanidin formation, and for the time being serve as a detoxicating mechanism. A full development of this conception would involve a consideration of the whole complicated matter of acid-base equilibrium of the body. One interesting feature of the hypothesis is its explanation of the mechanism whereby augmented protein metabolism, by increasing ammonia production, aggravates parathyroid tetany.

The fact that calcium salts alleviate tetany is explained on the ground that they decrease the permeability of the body cells and hence the taking up by them of guanidin.

On the other hand an increased excretion of lipoids by augmenting cell permeability increases guanidin intoxication.

The least convincing feature of the paper is a hypothesis that the body cells normally produce methyl cyanamide as a "hook," which they are able to dispatch to the parathyroids to obtain a supply of hormone necessary to their welfare.

The following therapeutic deductions are offered: Neither parathryoid grafts nor the administration of parathyroid substance are of much promise. Palliative methods are, therefore, alone generally possible. These are the administration of calcium—which has a limited usefulness—and administration of sufficient acid to depress the level of available ammonia below that necessary in the formation of guanidin. Only enough acid should be used to maintain "electric neutrality" of the blood.

The article is difficult to abstract and the original deerves the careful consideration of those who are interested from any point of view in the parathyroid glands.—R. G. H.

38. (PINEAL) The development of the paraphysis and pineal region in mammalia. Warren (J.) Jour. Comp. Neurol. (Phila.) 1917, **28,** 75.

A technical account of the development of the paraphysis and pineal body in man and other mammals.—E. R. H.

39. (PINEAL GLAND) Die Glandula Pinealis. (The Pineal Gland.) Uremura, Frankfurt. Ztschr. f. Path. (Wiesbaden) 1917, **20,** No. 3.

A very complete study on the histology of the pineal of the pineal gland (nothing new).

The author believes that there is a relation between the gland and the anterior lobe of the pituitary.

On some cases of adiposity the pineal gland and the anterior lobe of the pituitary were very large. In one case of gland. The author found brain sand in this gland in a child as young as four years. Description of three cases of tumor atrophy of the pineal gland there was also atrophy of the anterior lobe.—J. K.

40. (SEX) Sex studies. IX. Interstitial cells in the reproductive organs of the chicken. Boring (A. M.) and Pearl (R.) Anat. Rec. (Phila.) 1917, **13,** 253.

Interstitial cells were found in ovaries of adult chickens, but not in those newly hatched. They were found in testes of male chickens just hatched, but not in adults. The authors point out that absence of interstitial cells of the testis has been noted in many different mammals. They do not consider the testicular interstitial cells necessary for the male domestic fowl. They question the theory of the relationship between such cells and sex characters.—E. R. H.

41. (SEX) The early history of the germ cells in the armadillo, Tatsuia novemcincta. Vanneman (A. S.) Am. Jour. Anat. (Phila.) 1917, **22,** 341.

The germ cells in this form arise in the blastocyst close to the endodermic wall probably from the cells of this endoderm and then push in the endoderm of the future fore gut. In the 4 m.m. stage they leave the endoderm, and migrate along the mesentery and then enter the gonad. Germ cells were never found within the blood vessels.—E. R. H.

42. (SEX GLANDS) Ein Fall von Kongenitaler Anorchie. (A case of congenital anorchidism.) Wildholz (H.) Cor.-Bl. f. schweiz. Aertze (Basel) 1917, **47,** 1307.

There have been described seven cases in which people were born without testes. Wildholz publishes the eighth case of congenital anorchidism. The patient, a man of twenty years, showed a great development of the subcutaneous fat. The secondary sexual characteristics were not developed; the penis had the dimensions of that of a boy of 6-7 years. There was no prostate to be found. The X-ray photograph of the hand showed still detached epiphyses. The X-ray photograph of the skull showed an enlargement of the sella tursica.—J. K.

43. (SEX GLANDS) Die Steinachschen Forschungen über Pubertätsdrüsen und Geschleshtsmerkmale I, II. (The experiments of Steinach on the transplantation of the sex glands.) Boruttau (H.) Deutsche med. Wchnschr. (Berlin) 1917, **43,** 1454, 1484.

In this paper Boruttau describes the experiments of Steinach. Steinach transplanted ovaries in castrated males and testes in castrated females. The effect was that the animals changed their character; the male developed a female type, the females behaved like males. Steinach observed these animals for more than three years and saw that the males with ovaries were still smaller and had thinner bones than their

sisters. The females with testicles were much larger and had much heavier bones than the normal males. Steinach calls this "hyperfeminirung" and "hypermaskulirung."

Following Steinach's work transplantation of testicles into men who had lost these organs was attempted. The results have been brilliant; the psychical symptoms disappeared, the potency returned. (Lespinasse has made a similar observation.—R. G. H.)

Another very important experiment was carried out by Steinach. He exposed young animals to very small doses of Röntgen-rays; these worked as a stimulant; the mammary glands, the uterus and the fallopion tubes showed an enormous hypertrophy. The Graeffian follicles had disappeared and the connective tissue between them showed hypertrophy.

In a case of sexual precosity in a rat it was found that the hypophysis and the pineal gland were absolutely normal.

The experiments carried out by Steinach have proved that the hormones of the testis and ovaries have an antagonistic action. Steinach has castrated very young guinea pigs and then transplanted the testis and the ovaries in the abdominal muscles of one guinea pig. These animals were in most cases true hermaphrodites; they have testes and at the same time normal female mammary glands.

Immediately after this operation the guinea pig behaves like a male, but after some weeks he first becomes sexually indifferent and at last his behavior is perfectly female. This is followed again by indifference. About three months after the operation the masculine sexual characters return. These alternating sexual periods go on during the life of the animal.—J. K.

44. (SPLEEN) The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. XIV. Changes in the blood following diversion of the splenic blood from the liver. A control study of the effects of splenectomy. Krumbhaar (E. B.), Musser (J. H.) and Peet (M.M.) Jour. Exp. Med. (N. Y.) 1916, **23**, 87.

Dogs whose splenic veins have been ligated or transplanted into the inferior vena cava, or in which an Eck fistula had been made, develop: (1) an anemia which resembles that following splenectomy; (2) a rapid increase in the resistance of the red cells to hypotonic salt solutions preceding or coincident with the anemia. Resistance usually returns to normal at about the same time that anemia disappears. (3) an initial leukocytosis, involving at first the polymorphonuclear leucocytes and transitional cells.

Ligation of the splenic vein caused considerable atrophy of the spleen, but not necrosis or thrombosis. The other opera-

tions caused little or no change in the spleen.

The disturbances following these operations may be due to a loss of a certain volume of blood to the liver, or to the loss of a splenic hormone. As the authors suggest, "if the former is true, the method of production of the anemia still remains unexplained. It is evident, furthermore, that the latter theory has also no value unless it is assumed that this hormone must be activated by passage through the liver."

—H. W.

45. (SPLEEN) Blood dyscrasias associated with splenomegaly. Weis (J. D.) New Orleans M. & S. J., 1916, **69**, 9.

(General clinical consideration.)

46. (SPLEEN) Blood dyscrasias associated with splenomegaly. Parham (F. W.) New Orleans M. & S. J., 1916, **69**, 13.

(Etiology of splenomegaly.)

47. (SPLEEN) Observations on splenomegaly. Weis (J. D.) New Orleans M. & S. J., 1916, **69**, 135.

Of no endocrine interest.

48. (SPLEEN) The etiology and pathology of blood dyscrasias associated with splenomegaly. Lanford (J. A.) New Orleans M. & S. J., 1916, **69**, 3.

Clinical consideration; nothing new.

49. (SPLEEN) Atypical form of splenic diseases. Kanavel (A. B.) Ill. Med. Jour. 1916, **30**, 110.

Discussion of general clinical and operative conditions relative to disorders of the spleen.

50. (SPLEEN) The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. XV. The resistance to hemolytic agents of dogs in which the splenic blood has been diverted from the liver. Krumbhaar (E. B.) and Musser (J. H.) J. Exp. Med. (N. Y.) 1916, **23**, 97.

Ligation of the splenic veins, or transplantation of the splenic veins or portal vein (Eck fistula) into the inferior vena cava in dogs results in a lessened tendency to jaundice following injections of toluylenediamin or hemolytic immune serum. Splenectomized animals exhibit similar reactions. The anemia and increased resistance of the red blood cells following these operations are probable factors acting against the hemolytic agents used. The lessened tendency to jaundice is also due, according to the authors, in part at least, to a mechanical factor dependent on the course of the blood supply to the liver.—H. W.

51. SPLENITIS, report of a case. Wilson (T.) U. S. Nav. M. Bull., 1916, **10**, 674.

Reports a fatal case of splenic abscess.

52. (TESTIS) The internal secretion of the testes. Wheelon (H.) Interstate Med. J. (St. Louis) 1917, **24**, 1089.

The article is a "collective abstract" relative to the seat of origin of the internal secretion of the testes. From a consideration of the effects of pathological processes, castration, vasectomy, the action of the X-rays, testicular transplants and observations upon cryptorchid animals and men it is concluded that the testicular hormone has its origin in the interstitial cells or cells of Leydig present in the testes.—H. W.

53. (TESTIS) Seasonal changes in the interstitial cells of the testis in the wood chuck (Marnota morax). Rasmussen (A. T.) Am. Jour. Anat. (Phila.) **27**, 475.

The paper contains a good discussion of the general significance of the relationship between hibernation and interstitial cells. In the woodchuck the author finds that spermatogenesis progresses slowly during hibernation, increases suddenly for a month at the termination of this period, then drops nearly to zero after the period in which the female bears her young, after which time spermatogenesis increases again slowly until the following year. The development of interstitial cells on the other hand does not occur except during the spring and early summer. They reach their greatest size only after spermatogenesis has begun to lessen. The interstitial cells are smallest in late summer and autumn. The cytoplasm contains much pigment and some lipoid. In the spring the cells increase in size (especially the cytoplasm) and there is an increase in the amount of lipoids and fat.—E. R. H.

54. (THYMUS) Beiträge zur Kenntnis des thymotoxischen Serums. Ogata (M.) Acta. Schol. Med. (Kioto) 1917, **1**, 449.

Ten cc. of thymotoxic serum, obtained from rabbits immunized with dog's thymus were injected subcutaneously within fifteen days into nine dogs ten to sixty days old. Six control animals received a similar injection of normal rabbit serum. Growth was retarded in the animals treated with thymotoxic serum and the thymus was atrophied, with increase of the interstitial connective tissue. In nearly all the animals the bones were smaller and less dense and contained relatively more water and a smaller absolute amount of calcium oxide, magnesium oxide and phosphoric oxide. The percentage of total ash was somewhat smaller in five cases only. The injection of serum from rabbits previously treated with ovarian

tissue from the dog produced no effect on the thymus, indicating the specific nature of the thymotoxic serum.— Physiol. Abst.

55. THYMUS Menschliche Hungerthymus. (Thymus in a case of starvation.) Hart (C.) Virchow's Arch. f. path. Anat. und Physiol. (Berlin) 1917, **224**, No. 1.

A child of three days which died of starvation, showed an atrophy of the thymus; the weight of the gland was 5 grm. There was a fatty degeneration of the cells. The author believes that during fasting toxins are formed which have an influence on the thymus. In experiments on dogs he came to the same conclusion. (Previous observers have noted that the thymus is especially subject to atrophy in inanition.)—J. K.

56. THYMUS. Ist der postoperative Basedowtod ein Thymustod? (Is the postoperative death in Graves' disease caused by the thymus?) Melchior (E.) Berl. klin. Wchnschr. (Berlin) 1917, **54**, 35.

A very long article, to prove that the thymus plays no part in causing death after operation in Graves' disease. In 75-85 per cent of Graves' disease the thymus is large, but the cases in which there is no large thymus are very severe. The patients who die after operation never show the symptoms of a status thymicus but simply show a rapid increase of the symptoms of Graves' disease. The prognosis of operation is much worse in cases with a small thymus than with a large one.

—J. K.

57. THYROID, action of, upon the growth of the body and organs of the white rat. Herring (P. T.) Quart. Jour. Exp. Physiol. (Lond.) 1917, **11**, 231.

The results are in general agreement with those of Hoskins (Jour. Exp. Zool. 1916, **21**, 295). Larger doses were employed, and it is interesting to note that there was a greater degree of hypertrophy of some of the organs than was obtained by Hoskins.

Small doses fed daily have but little effect on the body growth as measured in length, but tend to diminished growth as estimated by body weight. Thyroid feeding causes enlargement of the suprarenals, heart, liver, spleen, testes and ovaries. There are no constant changes in the thymus. There is a decrease in the size of the pituitary in females. Kojima's statement (see abstract in this number of Endocrinology), that the pancreas is hypertrophied, is confirmed.

The uterus of the young rat appears to be checked in its growth, and as there is a similar check in the growth of the pituitary, the author thinks there may be a close correlation between these two organs.—T. C. B.

58. (THYROID) Studien über die Schilddrüse. XXX. Die Wirkungen auf den Darm. Eiger (M.) Ztschr. f. Biol. (Munchen) 1917, **67,** 372.

In connection with the diarrhoea accompanying Basedow's disease the effect of Burroughs Wellcome thyroid tablets was tested on the surviving rabbit intestine by the method of Magnus. Weak doses distinctly increased muscle tonus, stronger doses increased the strength of the contractions, while stand-still followed the use of very strong doses.—Physiol. Abst.

59. (THYROID) Influence of thyreodin on standard metabolism. Krogh (M.) Ugesk. f. Laeger (Kobenhavn) 1916, **52,** 4.

Determinations of the oxygen consumption have been made on urethanized frogs before and after administration of thyreodin and with and without division of the four nerve trunks for the limbs. From the fact that thyreodin causes a much smaller rise in metabolism after cutting of the nerves, it is provisionally concluded that it acts chiefly by increasing the tone of striated muscle.—Physiol. Abst.

60. (THYROID) Ueber die Wirkung der Schilddrüse auf den Blutkreislauf, II. Oswald (A.) Pflüger's Archiv. (Bonn) 1916, **166,** 169.

Further experiments to prove that iodothyroglobulin is the really active agent of the thyroid secretion. Its methylene derivative has similar actions; removal of the iodine weakens the effect, but if the iodine is added to it artificially the effect is not strengthened. Other iodine-holding natural products (gorgonin, spongin) act on autonomic nerves in the same way as the thyroid globulin, but not so markedly; the nucleoprotein of the organ or protein-free extracts have no effect.—Physiol, Abst.

61. (THYROID SPLEEN) Physiologie der Drüsen. L. Asher. XXXI. Ueber das Zusammenwirken von Milz, Schilddrüse, und Knockenmark. Du Bois (M.) Biochem. Ztschr. (Berlin) 1917, **72,** 141.

In some rabbits, the spleen, in others the thyroid, in others, still, both organs were extirpated; full details of the resulting blood picture are given in reference to colored corpuscles, leucocytes, lymphocytes, hemoglobin, etc., and of the response of such animals to oxygen want (injection of HCN). The general conclusion drawn is that both organs affect the bone marrow, the spleen being inhibitory and the thyroid stimulating it.—Physiol. Abst.

62. (THYROID) The treatment of goitre with quinine and urea injections. Watson (L. F.) Med. and Surg. (St. Louis) 1918, **2**, 49.

The quinine and urea injection has limitations the same as any other treatment for goitre and must be employed only in selected cases. It will not benefit the symptoms in those patients in whom the circulatory and nervous system have been permanently damaged. The treatment is contraindicated in fibrous and calcareous types of goitre; partial thyroidectomy is the only measure that will remove the tumor in these cases. The treatment of the exophthalmic type in young adults, especially in men, is difficult and should be attempted only under the most favorable circumstances. The treatment is surrounded by certain dangers, immediate and remote. One inexperienced is liable to puncture the treachea or one of the large blood-vessels, or to make the injection into the soft tissues of the neck. Injections that are too extensive will produce the same signs of myxedema that follow the removal of too much thyroid by operation. The necessity of minimizing the slight pain of any injection by means of local anesthesia cannot be too strongly emphasized. If the quinine and urea treatment is administered without preliminary injections of a few minims of sterile salt solution, followed by injections of sterile water, attacks of acute hyperthyroidism which might result disastrously, are liable to follow.

The gradual improvement of the exophthalmos in certain cases following the quinine and urea treatments points to a nerve control exerted by the thyroid on the exophthalmos.

Exophthalmic and non-exophthalmic goitre occur later in life in non-goitrous localities than in sections where the disease is prevalent.

The number of patients cured is highest in the group of those who came for treatment early in the disease; the benefit received by those who came later, was in proportion to the degree of damage done the circulatory and nervous systems. A goitre that has once disappeared has never recurred. A majority of the patients in this group have been under observation for two to five years.—Author's Summary.

63. (THYROID) Desquamation und Secretion in der Glandula thyreoidea. (Desquamation and secretion in the thyroid gland.) Guillebeau, Virchow's Arch. (Berlin) 1917, **224**, 217.

Small pieces of the thyroid gland from different animals were kept during one or two days in an incubator. They always showed an increase of the follicular epithelial cells. The author was able to observe the production of colloid by the cells.—J. K.

64. (THYROID) Blood picture in a case of Basedow's disease with parathyroid tetany. Sandelin (T.) Finska Läk. Handlingar (Helsingfors) 1917, **59,** 90.

In this case there were two operations; the second produced tetany and death. During tetany there was an increase of neutrophile leucocytes, and a fall in lymphocytes and eosinophiles. The coagulation time was delayed. The picture is that of sympathetic stimulation.—Physiol. Abst.

65. (THYROID) Beiträge zur Physiologie der Drüsen. Leon Asher. XXIX. Nachweis der Stoffwechselwirkung der Schilddrüse mit Hilfe eines eiweissfreien oder jodarmen Schilddrüsenpräparates. Abelin (J.) Ztschr. f. Biochem. (Oldenburg) 1917, **70,** 259.

"Thyreoglandol-Roche" is a derivative of thyroid gland which is soluble in water, free from protein and contains little iodine. When added to a nitrogen-poor diet, it caused a rise in the nitrogen output of a bitch. A similar increase occurred after its administration to the fasting animal. After thyroidectomy (parathyroids intact) a precisely similar rise in the nitrogen output followed the ingestion of thyreoglandol by the fasting animal and this result was confirmed on a thyroidectomized dog. The reaction is not constant in the normal animal, and was absent in a control bitch. Identical effects were produced by the similar administration of Burroughs and Wellcome's thyroid tablets. It is evident that the stimulation of metabolism which is the characteristic feature of the thyroid is not associated with protein, and is not dependent on the amount of iodine present.—Physiol. Abst.

66. (THYROID) Beiträge zur Physiologie der Drüsen. Leon Asher. XXX. Untersuchungen zur Frage ob nach extirpation von Schilddrüse und Nebenschilddrüsen biologisch nachweisbare toxische Stoffe im Blute auftreten. Backman (E. L.) Ztschr. f. Biolog. (München) 1917, **67,** 353.

Thyroidectomy or parathyroidectomy was performed on six rabbits, and after the development of the typical symptoms the animals were killed and the action of their serum and plasma were tested on the isolated intestine of the normal and operated rabbit. In neither case was there a specific effect on the automatic movements of the bowel; the presence of proteinogenic amines and alkaloids in the blood in thyreopriva tetania is thereby excluded. The intestinal movements and reaction to adrenin of the operated animals resembled the normal. Normal oxalated plasma is without effect on the isolated bowel; there is a late secondary increase of tonus due to sodium oxalate and to coagulation of the plasma. Blood

serum, on the other hand, with or without oxalate, causes an immediate increase in the tonus and height of the contractions.—Physiol. Abst.

67. (THYROID) Experimentelle Studien über die Schilddrüse: (1) Der biologische Nachweis der inneren Sekretion der Schilddrüse im Blute der mit Schilddrüsenextracten gefütterten weissen Ratten; (2) Der biologische Nachweis der inneren Sekretion der Schilddrüse im Blute der Schilddrüsenvene sowie auch in der Blutbahn der Basedow-Kranken. Eiger (M.) Ztschr. f. Biol. (München) 1917, **67**, 253, 265.

The augmenting action of thyroid secretion on adrenin can be demonstrated on the Laewen-Trendelenburg frog by first determining the subminimal dose of adrenin. The subsequent injection of the latter with a diluted and inactive extract of thyroid gland or preparation causes a marked constriction of blood vessels.

Ordinary plasma (oxygenated three to five hours) from dogs, normal and goitrous men, has no activating action on the subminimal dose of adrenin, unless it be obtained from the inferior thyroid vein, when it gives a positive reaction. The plasma of rats fed on thyroid for considerable periods, and plasma obtained from seven patients suffering from Basedow's disease had a well-marked activating action on adrenin, thereby demonstrating the presence of thyroid secretion in the blood in these conditions.—Physiol. Abst.

68. (THYROID and PITUITARY) Beiträge zur Physiologie der Drüsen. Leon Asher. XXVIII. Die Einwirkung von Thyroidea und Hypophysisextrakten auf die Nierengefässe, Backman (E. L.) Ztschr. f. Biol. (München) 1917, **67**, 327.

The effect of intravenous injections of thyroid and pituitary extracts on the general blood-pressure and volume of the kidney were studied in four rabbits narcotized with urethane. The vagi were cut to obviate shock and two of the animals were eviscerated. The blood pressure in every case was unaffected by thyroid tabloids; an occasional rise was noted with "thyreoglandol." In the eviscerated animal (exhibiting the primary effect of thyroid extract) the renal vessels were always dilated, but dilatation or no change were observed in the intact animal. Single and repeated doses of "pituglandol" and "pituitrin" caused a considerable slow and lasting rise in blood-pressure. Constriction of the renal vessels was the constant result in the eviscerated animal, but it alternated with dilatation in the intact animal. Neither extract had any demonstrable effect on artificial splanchnic stimulation.—Physiol. Abst.

69. (THYROID) Changes in the central nervous system in hypothyroidism, Mott. (F. W.) Proc. Roy. Soc. Med. (Lond.) 1917, **10,** 51.

There is a universal chromatolytic change in the cells of the central nervous system. A marked case of myxedema is described in which the changes are figured. In the pituitary, the pars intermedia showed excess of colloid, but this is not regarded as evidence of vicarious relationship. The lipoids in the suprarenal cortex were diminished.—Physiol. Abst.

70. (THYROID) Anabolic action of the thyroid gland, Janney, (N. W.) Proc. Amer. Soc. Biol. Chem. Jour. Biol. Chem. (N. Y.) 1917, **29,** 6.

Thyroid in large doses exerts a catabolic action characterized by toxic symptoms and by a great increase of all the urinary nitrogenous constituents except creatine. The anabolic action of small doses of thyroid administered to cretins and exophthalmics over extended periods was accompanied by an added retention of nitrogen and an improvement in the symptoms.—Physiol. Abst.

71. (THYROID) Three children with sporadic cretinism, in one family. Herrman, (C). Arch. Pediat. (N. Y.) 1917, **34,** 831.

This is the second series of three cases of sporadic cretinism occurring in one family to be reported by Herrman, the first appearing in N. Y. State Jour. Med. Aug. 1914.

He gives a good clinical description of the three patients who were 22 (female), 20 (male), and 18 (female) years old respectively. They were all backward in physical and mental development, and gave a history of having been under intermittent treatment since three years of age. They were all breast fed from eight to sixteen months and showed signs of deficiency early, these being manifested by delay in teething, sitting and walking. He placed them on a combination of thyroid, pituitary and suprarenal extracts, obtaining marked improvement in 2½ months.

The parents were not related in this series, but they were in the first. Herrman found consanguinity in only five cases out of 50 which have come under his observation. He thinks that anomalies of the so-called ductless glands can be best explained on the basis of heredity and that there is probably some defect in the function of the endocrine system in the ancestry of these children.—M. B. G.

72. THYROID extract in hydrocephalus. Elsberg (C. A.) Arch. Pediat. (N. Y.) 1917, **34,** 851.

In a paper on "Chronic Internal Hydrocephalus, the Newer Methods for Its Recognition and Treatment," read before the Section on Pediatrics of the New York Academy of Medicine, Elsberg stated that there are three definite types of hydrocephalus: that due to obstruction, that due to diminished absorption and that due to hypersecretion. For the differentiation of these types, he used phenolsulphonaphthalein as an indicator. He advised that in cases of hydrocephalus due to hypersecretion, a lumbar puncture should be done every few days, and the patient should be given thyroid extract in doses up to the physiological limit. A certain number of satisfactory results could be obtained by this combination of thyroid feeding and repeated lumbar punctures in this type, but very little improvement had been seen with this treatment in hydrocephalus due to diminished absorption.—M. B. G.

73. THYROID. Studies of the changes in, caused by pituitary extract. Pardi, (U) Lo Sperim., Jan. 1916. Abstr. Arch. Pediat (N. Y.) 1917, **34**, 802.

The object in view was to determine whether modifications of the structure of the thyroid could be caused by pituitary extract alone or by other organic extracts as well. Hallion and Alquier investigated the matter some time before. Pardi had under observation four groups of rabbits, 31 in all. They were treated with intramuscular injections of extracts of spleen, pituitary body and liver. The daily dose was 2 cc. injected in the gluteal region. Twenty-four hours after the last dose the animals were killed. Results: (a) Changes of structure in thyroid were practically the same following the injections of the various extracts. (b) Changes indicate colloid hypersecretion and not hyposecretion. (c) The action of the extracts employed caused vasomotor symptoms by stimulating either directly or indirectly the secretion of colloid substance. —M. B. G.

74. (THYROID) Attempts to produce experimental thyroid hyperplasia. Burget (G. E.) Am. Jour. Physiol. (Balt.) 1917, **44**, 492.

The experiments were undertaken to determine certain factors that have been reported to induce thyroid hyperplasia in men and experimental animals.

The author finds that a high protein diet develops hyperplasia of the thyroid in rats. If kept under unhygienic conditions, rats develop hyperplasia of the thyroid on a standard diet of bread and milk; and a combination of high protein diet with unhygienic conditions gives a greater degree of hyperplasia than either method alone. Young growing rats on a high protein diet do not develop hyperplasia.

The influence of feces from goitre patients and from goitre dogs was tried out on cats, since these animals seldom have goitre when brought to the laboratory, or develop it when kept under laboratory conditions. About 100 cc. of a solution of feces from a goitrous dog, and from a case of exophthalmic goitre, seemed to have no effect.

Suturing the right phrenic with the right cervical sympathetic after the method of Cannon, Binger and Fritz gave negative results, as far as hyperplasia of the thyroid was concerned. The same is true for the removal of a portion of the cervical sympathetic.—T. C. B.

75. (THYROID) Cretinism and Chagas' disease. (Second communication) Kraus (R.) and Rosenbush (T.) La Prensa Med. (Buenos Aires) 1916, No. 17. Correction, Endocrin. 1917, **1**, 376.

The authors show that the goitre occurring in Argentine is not produced by Trypanosoma Cruzi.—B. A. H.

76. (THYROID) Tuberkulose der Schilddrüse mit besonderer Berücksichtigung der Tuberkulose in Basedow-Schilddrüsen (Tuberculosis of the thyroid and exophthalmic goitre.) Urmara (S.) Deutsche Ztschr. f. Chir. (Leipzig) 1917, **140**, 324.

Urmara has observed some cases in which a tuberculous infection was followed by Graves' disease. The author believes that the toxin of the tubercle bacillus can stimulate the secretory activity of the thyroid gland. If a patient with Graves' disease is infected with tuberculosis the symptoms increase rapidly.—J. K.

77. (THYROID) Die Erfolge ausgiebiger Schilddrüsenresektion bei Morbus Basedow. (The surgical treatment of exophthalmic goitre.) Lick (E.) Deutsche Med. Wchnschr. (Berlin), 1917, **43**, No. 42.

The author maintains that surgical extirpation is always the treatment of choice in exophthalmic goitre. Upon the appearance of exaphthalmos most of the thyroid gland should be removed at once without waiting for the appearance of any other symptoms. X-ray treatment has little effect. Splendid results have been observed when extirpation has been followed by injections of quinine and urea into the part of the gland not removed.—J. K.

78. (THYROID-SEX GLANDS) Uber das Verhalter der genitalen. Funktionen beim Myxoedem des Weibes. (The sexual functions in women suffering from myxoedema.) Veil (W. H.) Arch. f. Gyn. (Berlin) 1917, **107**, 199.

Description of two cases of women with normal sexual functions in whom a strumectomy was performed. In both cases too much of the gland was taken away and the symptoms of myxoedema developed. The menstruation became irregular, both women showed all symptoms of a true menopause, the uterus became smaller and at last menstruation ceased. In both cases a perfect recovery was observed after administration of thyroid gland.—J. K.

79. (THYROID) Kohlehydratstoffwechsel bei Erkrankungen der Drüsen mit inneren Sekretion. (Carbohydrate metabolism and diseases of the endocrine organs.) Ritter (F.) and Weiland (W.) Ztschr. f. exper. Path. u. Therap. (Berlin) 1917, **19**, 118.

It was the intention of the authors to study the carbohydrate metabolism in different cases of disease of the endocrine organs. Because of the war they could not continue their experiments. Therefore they now publish only their experiments with patients suffering from diseases of the thyroid gland. In myxoedema they found a high amount of blood sugar; in one case even 0.198 per cent. In Graves' disease they found it very low and glycosuria was never observed to occur after administration of 100 gms. of glucose or laevulose by mouth. In all cases of myxoedema 300 gms. of glucose were enough to cause glycosuria. They observed once more the well known fact that after intravenous injections of sugar in cases of myxoedema, it took a greater time for all of the sugar to be execreted in the urine than in cases with normal or hypertrophic thyroids.—J. K.

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